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Of Special Interest to CONTRIBUTORS

Contributors to MEDICINE will receive twenty-five reprints of their articles free of cost. Due to the unusual nature of the periodical, additional reprints will not be available.

Since it is anticipated that it may prove desirable to publish certain articles as separate monographs, it has been arranged with the Publishers to allow to contributors a royalty on the sales of such monographs.

FOREWORD

The rapid advances taking place at the present time in medicine in many different countries, and the publication of studies in a great number of periodicals and in different languages, make it difficult for practitioners and students to keep abreast of modern knowledge, and to estimate accurately the value of the numerous contributions constantly appearing. This has long been recognized to be true and attempts have been made in other countries to provide authoritative reviews in the different fields of medical science. There has been no such attempt at comprehensive reviews in the field of clinical medicine in the English language. It is the aim of MEDICINE to provide such reviews of internal medicine, neurology and pediatrics, and of subjects in the border zone between medicine and surgery.

The reviews will not be restricted as to length, but an opportunity will be given adequately to discuss a disease, or certain aspects of disease or subjects that allow a better comprehension of disease processes.

The reviews will be issued quarterly.

Each volume will consist of approximately 500 pages.

The selection of subjects and authors will be made by the Editors.

All correspondence relating to the publication of papers should be addressed to the Associate Editor, DR. PAUL D. WHITE, Massachusetts General Hospital, Boston, Massachusetts.

DAVID L. EDSALL,
JOHN HOWLAND,
Editors.

THE THERAPEUTIC USE OF DIGITALIS

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I. INTRODUCTION

Digitalis was introduced into medicine by William Withering (163), who published at Birmingham, England, in 1785, his book entitled "An account of the foxglove and of its medicinal uses, with practical remarks on dropsy and other diseases." This book deserves a place among the medical classics, not only because it introduced digitalis into medicine, but also because it reveals an attitude of mind which should serve as a model for all who wish to bring forward any new therapeutic agent.

The words of Withering form a fitting introduction to this review. He says:

It is much easier to write upon a disease than upon a remedy. The former is in the hands of nature, and a faithful observer, with an eye of

tolerable judgment, cannot fail to delineate a likeness. The latter will ever be subject to the whims, the inaccuracies and the blindness of mankind.

Withering's views on pharmacology did not differ widely from those of today, as is indicated by the opening paragraphs of his account of foxglove.

As the more obvious and sensible properties of plants, such as color, taste and smell have but little connexion with the diseases they are adapted to cure, so their peculiar qualities have no certain dependence upon their external configuration. Their chemical examination by fire, after an immense waste of time and labour, having been found useless, is now abandoned by general assent. Possibly other modes of analysis will be found out, which may turn to better account, but we have hitherto made only a very small progress in the chemistry of animal and vegetable substances. Their virtues must therefore be learnt, either from observing the effects upon insects and quadrupeds; from analogy, deduced from already known powers of some of their congenera, or from the empirical usages and experience of the populace.

The first method has not been much attended to, and the second can only be perfected in proportion as we approach toward the discovery of a truly natural system; but the last, as far as it extends, lies within the reach of every one who is open to information, regardless of the source from whence it springs.

It was a circumstance of this kind which first fixed my attention on foxglove.

Withering indicates, at the outset, some of the various phases of study through which digitalis was destined to go. First, the empirical studies which have almost invariably marked the beginning of progress in therapeutics. Second, the study of the effects of the drug in lower animals, the period of experimental pharmacology. Third, the study of the effects of the drug on man by exact methods which allow observations approaching in accuracy those made on lower animals, the recent, present-day period. The relation of chemical structure to pharmacological action, although "abandoned by general assent" in Withering's day, represents the pharmacology of the future, which is today beginning to show far-reaching possibilities.

As far as digitalis is concerned, however, scarcely a beginning has been made.

The literature on digitalis and its allies is very extensive, and an attempt to cover it completely has not been made. This review will include the more recent work dealing especially with the action of the drug on man, and particularly on patients suffering from heart and circulatory diseases. The literature of experimental pharmacology will be reviewed only in so far as is necessary to lead up to and explain the effects of digitalis as observed in therapeutics. There remain certain points which are better known on animals and the direct application of experimental results is necessarily made, in some instances, in the therapeutic use of digitalis. The direct application has certain difficulties which will be pointed out, and as the methods for studying the effects of the drug on patients become more and more exact, the application of experimental facts becomes less and less necessary. The relation of experimental pharmacology to the therapeutic use of digitalis will be discussed subsequently.

II. HISTORICAL DATA

Foxglove was first "noticed" according to Withering (163) by Fuchsius in 1542, who gave it the botanical name Digitalis purpurea because of the resemblance of its flowers to a finger or a thimble ("finger-hut") and because of its purple color. Fuchsius also mentioned the emetic action of the plant when eaten. Boerhaave considered foxglove a poison but Alston held that it was one of the native plants of England which should be considered a medicine of great virtue. Haller mentioned foxglove as a purge. Withering also relates the observations of Salerne, who made apparently the first experiments with the plant on animals in 1748. He fed the leaves to turkeys and described both the fatal and non-fatal effects which he observed. The emetic and purgative effects of foxglove were known before Withering's time, and the plant had been used in ointments and also as an expectorant.

Withering undertook the use of foxglove because he was informed of a secret remedy by which an old woman of Shropshire was often able to relieve and cure patients with dropsy to whom no help could be given by some of the leading medical men of the day. He obtained

the formula which she used, consisting of some twenty herbs, and from his knowledge of medicinal plants, concluded that foxglove was the one whose action was beneficial. Withering's book was written after an experience with the drug covering a period of ten years. He gives an account of one hundred and sixty-three patients to whom he had given the drug, and also published communications from other physicians whom he had told of his early results. He states that in order to prevent any unwarranted enthusiasm for the drug, he has reported all patients to whom the drug was given without selection, and warns his readers from being led astray by the communications of other physicians from whom he had received reports of selected cases. The case reports are concise, clear and graphic but, strange to say, deal exclusively with the diuretic effects of the drug and the disappearance of dropsy. Withering observes the fact that digitalis slowed the pulse, especially when given in large doses, but he did not associate this effect with the benefit of patients suffering from heart disease. In fact it is evident that he considered the diminution of the heart rate as a sign that the maximum dose of the drug had been given, for he says: "Let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects." This is sound advice, which for many years, has been disregarded.

The appearance of Withering's book one hundred and thirty-seven years ago represents the beginning of the period of study of digitalis by direct observations on patients, the drug being given for purely empirical reasons. The manner or method of its action were unknown and there were but few established facts on which to base hypotheses.

Cushny, Morris and Silverberg (32) have given a brief review of the varying opinions regarding digitalis following the publication by Withering. In 1799 Ferriar published "An essay on the medical properties of Digitalis purpurea or foxglove" in which he said that "the power of reducing the pulse is the true characteristic" of the drug, diuresis being a less constant and a less essential quality of the plant.

Beddoes in 1801 stated that "in a certain dose, digitalis will increase the activity of the arterial system." In this same year, Kinglake also showed that the force of the pulse was increased by the drug; and in

1839, according to Cushny, Blake discovered that digitalis caused an elevation of blood pressure. In spite of these observations, digitalis was generally considered a cardiac sedative. Its use was advised by Pereira in 1840 in cases of pulmonary hemorrhage and aneurism. This idea was supported by Traube, who discovered that digitalis stimulated the vagus nerves during his pioneer experiments on animals in 1851, but it was abandoned after Schmiedeberg's (138) classical work published in 1874, which showed the effect of digitalis on the frog's heart. A comprehensive view of the history of the pharmacology of digitalis up to 1883 is given by Schmiedeberg (139) and will not be taken up here.

In spite of the masterly presentation of Withering, digitalis did not gain a firm foothold in medical practice until recent years. Pratt (122) has reviewed the various treatises on heart disease written by eminent English authors, in order to find out the dependence that was placed in the drug. Beginning with Allan Burns, who in 1809, published the first general treatise on heart disease, and going through Hope, Stokes, Latham and Walshe, as well as our own Austin Flint, he found that they paid little or no attention to Withering's teaching and never discovered for themselves the great value of digitalis in cardiac failure. Pratt is unable to say who deserves the credit for impressing upon the medical world the value of Withering's work. He says, however, that "Sir James Mackenzie, working over a hundred years later, was the first clinician to demonstrate conclusively the correctness of Withering's instructions regarding the administration of digitalis."

III. THE DIGITALIS GROUP

There are a number of drugs which resemble digitalis more or less closely from the point of view of their pharmacological action, which are usually included in the so-called digitalis group. They act upon the heart muscle and the musculature of arteries and stimulate certain nervous structures including the vagus centre. In this group are to be included digitalis, strophanthus, squill, apocynum, convallaria, adonis, hellebore and oleander. Abel and Macht (1) have isolated a digitalis-like body from the poison of the tropical toad, Bufo agua. They call this substance bufagin. Its marked action on the heart,

its vaso-constrictor action and its powerfully stimulating action on the vagus centre led them to class this drug with the most effective members of the digitalis series. Many substances, of which barium may serve as an example, have a superficial resemblance in their action to digitalis, but should not be considered as members of the group. The characteristic digitalis effects are produced in experimental animals by all the drugs that belong properly in the group, the difference between them being quantitative. For this reason the various members of the group have been used more or less interchangeably in experimental work. In their use in clinical medicine, differences have been discovered, especially in dosage, rapidity and duration of action and absorption from the gastro-intestinal tract which makes their differentiation important.

As digitalis and strophanthus are by far the most important drugs of the group from the therapeutic standpoint, this review will deal with them almost exclusively.

1. Digitalis

The drug is usually derived from the leaves of Digitalis purpurea. The leaves are gathered and dried and then the drug is prepared for use by powdering the leaves or by extracting their active principles by water, alcohol or other solvents. Digitalis and its active principles have been prepared in many forms for therapeutic purposes and the best known of the preparations will be discussed when the question of the administration of the drug to man is considered.

The active principles contained in Digitalis purpurea were first studied by Schmiedeberg (138). He found that from fresh digitalis leaves, at least three active glucosides could be obtained which he called digitoxin, digitalin and digitalein. Digitoxin is the most highly active of these substances, and produces all the characteristic pharmacological effects. It is practically insoluble in water, but is easily soluble in alcohol. Roth (136) has recently given a brief review of the chemical investigations of the digitalis bodies. He says that Kiliani, who has made the most important chemical study of digitalis, gives $C_{34}H_{54}O_{11}$ as the formula for digitoxin, while the true or crystallized digitalin has the formula $C_{35}H_{56}O_{14}$. Digitalin is easily

soluble in alcohol and very slightly soluble in water. It is found in larger quantities in the seeds than in the leaves of digitalis.

The term "digitalin" has been used to denote a variety of preparations which has served to bring into the literature considerable confusion. Hatcher and Eggleston (78) state that the name is meaningless without a qualifying term, and it has been used to mean digitoxin, true digitalin, or a mixture of the latter with digitonin, a saponin-like substance. Other instances of such confusion are found in the literature dealing with the digitalis group. This is much to be regretted and careful consideration should be given to this question of terms. A general agreement in this connection is much desired.

Digitalein is a water-soluble glucoside which Schmiedeberg considered a pure substance, while Kiliani looked upon it as a mixture.

Besides the active substances that have been mentioned, digitalis also contains a saponin-like body called digitonin. It is inert as regards the characteristic digitalis effects, but according to Roth (136), it is due to the digitonin that aqueous solutions of digitalis leaves contain the water-insoluble substances, digitalin and digitoxin.

As stated by Roth, Kraft in 1912 isolated from a watery extract a glucoside which he named "gitalin" which he considered a purified digitalein. Both Kiliani and Rosenthaler worked with gitalin in 1914, and concluded independently that it was not a definite substance and could be resolved into constituents having unlike chemical and pharmacological properties. Several other investigators have attempted to shed further light on the chemical constituents of digitalis and in 1913 Kolipinski isolated an acid resin which he named "digitalic acid." He concluded from his many animal experiments that "digitalic acid" possessed all the virtues, without any of the poisonous properties of digitalis when used in therapeutic or larger doses. He also considered that it produced no cumulative effects and was not irritating when used subcutaneously. The work of Kolipinski would have held promises of definite advance in the therapeutic use of digitalis, if it had been confirmed by further study, but the investigations of Sharp and of Smith in 1914, failed to substantiate Kolipinski's claims, as both reached the conclusion that digitalic acid has no pharmacological effects whatever, being an inert substance.

2. Sources of digitalis

For many years, the English-grown leaf, especially those marketed by Allan, was considered the standard source. During recent years, however, the greater part of the supply of digitalis used in the United States came, according to Roth (135), from Germany and Austria. When this source of supply was cut off during the years following 1914, by the turmoil of war, attention in the United States was turned to the home-grown product. Wilbert pointed out that Digitalis purpurea grew abundantly in California, Oregon and Washington and, to some extent, in West Virginia. In these states, it is found growing wild, and is considered a "weed" in various parts of the country. American leaves were used by Rowntree and Macht (137) in 1916, who prepared infusions from them as well as from European leaves, and when the pharmacological activity of these infusions was determined on cats they found that the highest potency was possessed by the infusions of American leaves.

Roth (135) investigated the activity of wild American digitalis in 1917 using leaves gathered in the States of Oregon and Washington. The leaves were air-dried and tinctures were made of them, the assays being conducted by the one-hour frog method. He found that the wild digitalis from the Northwestern States was of sufficient strength to allow its use as a source of supply in making the various official preparations of digitalis, and he concluded that by the use of ordinary methods in handling and preparing the leaves, a highly active product could be secured which compared favorably with the activity of cultivated leaves grown under more favorable conditions.

A new species of the American-grown plant, Digitalis lutea, has recently been employed and its efficiency tested on both animals and patients. White and Morris (139) have used this form of digitalis grown in Minnesota, and have compared its activity with Digitalis purpurea. They find that Digitalis lutea possesses the same therapeutic value as purpurea and seems to have less effect on the gastrointestinal tract. Christian (16) reports that he has had excellent clinical results with American-grown digitalis, and Pratt (122) who has used both American-grown purpurea and lutea, says that active leaves grow in various parts of the United States from Maine to the Pacific Coast.

Pratt and Morrison (123) tested out twenty-five samples of American grown digitalis by the one-hour frog method, using both purpurea and lutea. Their work shows that the best American digitalis, both wild and cultivated, is equal in activity to the best European digitalis. They obtained specimens of high potency from Virginia, Nebraska, Wisconsin, Minnesota, Oregon and Washington. There was, however, a definite difference in the potency of various samples, and seventeen out of twenty-five were below the standard of strength required by the United States Pharmacopeia. The average strength of the American-grown leaves was greater than that of the various imported leaves examined. Pratt and Morrison suggest that samples from a crop of digitalis should be tested biologically before it is gathered in large quantities for therapeutic use.

It may be considered as established that digitalis of good potency grows in America in both the wild and cultivated state so that dependence need no longer be placed upon the European market. The species Digitalis lutea seems also at least as useful as the Digitalis purpurea, and may prove to have some advantages over the better known species.

3. Strophanthus

This drug was introduced into medicine by Sir Thomas Fraser (55), who discovered it during an investigation of the arrow poisons used by certain African tribes. Several variations of the plant Strophanthus Kombé, S. hispidus, S. Gratus, and others contain the active principle of the drug, the seeds being especially rich in it, and are used in making the various preparations for therapeutic use. Hatcher and Eggleston (78) have pointed out the uncertainty of origin of much of the strophanthus of commerce, and state that they are not convinced that all commercial specimens of strophanthus—even those obtained from reputable dealers—are sold under their correct botanical names. This is perhaps more of an academic question than one of importance from the point of view of therapeutics, as the active principle, strophanthin, appears to be identical in its pharmacological properties, regardless of its source. Hatcher and Eggleston state that the active principle, strophanthin, has also been considerably confused. The term is properly employed only as

applied to amorphous strophanthin, but it has also been used for ouabain and "crystalline strophanthin-g." Ouabain is a crystalline substance obtained from strophanthus and represents the purest chemical substance, possessing the most potent activity of any body belonging to the digitalis group. It was isolated in 1888 from ouabain wood by Arnaud, who gave it its name and established its identity with that of the active substance obtained from Strophanthus gratus. This same substance was called by Thoms sixteen years later "crystallized strophanthus-g." As amorphous strophanthin and crystalline strophanthin or ouabain are both used therapeutically and may differ much in potency, this confusion of names is very unfortunate and should be avoided.

Strophanthus and its active principle possess all the pharmacological properties of digitalis, and the solubility and potency of strophanthin and ouabain make them important members of the digitalis group, being especially valuable for intravenous administration.

4. Other members of the group

Other members of the digitalis group have not a well established place in therapeutics, although some of them have been extensively used. Recently the action on man of several members of the group have been studied by modern methods by White and his collaborators. Squills, apocynum and convallaria have been administered to patients in whom the action of these drugs was compared with that of digitalis. These studies will be referred to when preparations are considered, but it may be stated at this time that they showed several reasons why these drugs are not as suitable, not as efficient as digitalis, and that they should not be used in the treatment of heart disease. Less is known about other members of the group. For these reasons the discussion of their action and their therapeutic use will not be included in this review.

IV. THE POTENCY OF THE DIGITALIS BODIES

1. The biological assay

The determination of the potency of a drug by quantitative chemical analysis is seldom feasible when the activity of the drug depends upon the presence of one and often of several chemically complex substances.

This has proved especially true of members of the digitalis group to which biological or pharmacological assays have long been applied. According to Hamilton (65) the earliest recorded attempt to standardize digitalis bodies by means of their effects when injected into animals was that of Fagge and Stevenson in 1866. The drug is administered to an animal in such a way that the amount necessary to produce a clearly defined and constantly occurring phenomenon can be accurately measured. By this method of assay the potency of various members of the digitalis group can be compared, and the various preparations for therapeutic use can be standardized.

A number of methods for the biological standardization of digitalis have been employed. Generally speaking, they depend on the determination of the minimal amount of drug required to kill the animal used. This method has been objected to as inapplicable to therapeutics as physicians do not want to kill their patients but to cure them. Hatcher (67) has made the following reply to this criticism:

> While it is perfectly true that physicians do not wish to kill their patients, it is equally true that the action of digitalis which they utilize in curing them is that which kills if it be carried too far, and it seems to me that it would be quite as logical to object to testing the strength of strands of cable by raising the tension to the breaking point, on the ground that engineers wish the cable not to break, as it is to object to the method in vogue for testing the activity of the digitalis bodies on the grounds mentioned.

There seems to be no better method of standardizing the digitalis bodies than that which depends on their power to kill.

The animals most commonly used for biological assays of digitalis bodies are the frog, the cat and the guinea pig, although the dog and the rabbit have been used by some experimenters, and one method has been suggested which depends on the determination of the minimal lethal dose for gold fish. The original method used by Fogge and Stevenson depended, according to Hamilton (65) upon the time required for the systolic stoppage of the exposed heart of the frog, after the drug was injected subcutaneously into the thighs. This general principle has been widely applied, and it has been recently especially elaborated and advocated by Focke (53). The frog test as employed

in 1916 (Roth, 136) by the Hygiene Laboratory of the United States Public Health Service, aims to determine the quantity of digitalis which will produce permanent systole of the ventricle, in an hour, when injected into the ventral lymph sac. Certain conditions, such as temperature at which the tests are carried on, the concentration of the injected fluid and its alcohol content, are kept constant. Roth states that a very disturbing factor in the one-hour frog method is that of absorption. The assay of digitalis by the frog method has been used with a number of modifications. In determining the minimal dose causing permanent systolic stoppage, the heart is necessarily exposed after the frog has been pithed, while in determining the minimal lethal dose this is not done. Hamilton (65) who has recently reviewed all the various methods of biological assay of digitalis that have been employed, apparently prefers the frog method and considers that there are advantages in determining the minimal lethal dose, namely, that less work and time are involved, that the factor of slow absorption is eliminated and that the end-point of the test is not obscured by rough handling necessitated by the pithing and laying bare of the frog's heart. However, in testing digitalis, it is not the general toxicity as much as the potency of the drug on the heart itself that is the essential feature, and therefore the systolic stoppage method with the heart exposed should be considered that giving the more exact information.

Hatcher and Brody (74) in 1910 proposed their cat method of standardization. This method determines the minimal lethal dose per kilogram of cat when the drug is injected slowly into the femoral vein. This amount, these authors have termed "the cat unit." For crystalline ouabain, the cat unit has been found to be 0.1 mgm., this amount of the drug per kilogram of cat being fairly constantly fatal when injected during a period of about ninety minutes. In testing other digitalis bodies Hatcher and Brody found that the accuracy could be increased by the following procedure. A measured amount of the digitalis body (tincture or infusion of digitalis, or digitoxin) is injected into the femoral vein in the first period of about ten minutes and after an interval of twenty minutes, the injection is resumed but a solution of crystalline ouabain is substituted for that of the digitalis body. This injection is continued slowly until the death of

the animal occurs. The difference between the amount of crystalline ouabain actually used to complete the assay and 0.1 mgm. per kilogram of animal (the amount which would have been required in the absence of the digitalis body) represents the activity of the digitalis used. There are certain precautions which the authors state, especially regarding the selection of animals, which should be followed. This method was adopted after the authors had assured themselves that ouabain was capable of replacing the other digitalis bodies.

The cat method is given in detail because of its increasing popularity especially with those administering digitalis accurately and carefully to patients. It is suitable for the standardization of the generally used therapeutic preparations, such as the tincture of digitalis, and can be carried out in any properly equipped laboratory, but its use by the retail pharmacist, as suggested by the authors, seems to the writer, to be, generally speaking, somewhat idealistic although highly desirable. The method has been criticized by Eckler (35) as complicated, time-consuming and expensive, and he points out a number of unknown factors that are involved, but he concedes that it has one point of superiority over all other methods in that the matter of absorption is entirely eliminated.

Macht and Colson (105) express as their opinion that the "cat method" gives more uniform results than the frog method, but they found that the fatal dose varies considerably in cats. They conducted two series of experiments: one in which the vagi were cut while the nerves were left intact in the other. Using digitalis, digitalin and strophanthin, they found that the results were more uniform in the series in which the vagi had been cut, but that the drugs were more toxic for these animals.

Hamilton (65) states that "the cat method is purely a toxicity test and can be classed with that on guinea pigs as objectionable because death is almost invariably due to paralysis of the respiratory center and therefore, not directly a measure of the heart toxic value." The experience of the writer with this method is not in accord with this statement. Respiratory changes practically always occur after the heart has ceased to beat, as revealed by the electrocardiograph. Auscultation of the cat's heart is also a helpful method of determining the end-point of the experiment, when digitalis is being injected intravenously.

Eggleston (41) has published a criticism of the cat method of Hatcher and has compared it with the twelve-hour frog method of Houghton, the one-hour frog method of Famuleuer and Lyons, and the guinea pig method of Reed and Vanderkleed. He discusses in detail the various factors which he considers important in the choice of a method for the biological standardization of the digitalis bodies. Eggleston concludes that there is no perfect or ideal method, but that each of the four methods discussed has certain advantages not possessed by the others. He considers, however, that the cat method of Hatcher possesses the greatest number of advantages which are as follows:

(*a*) It is accurate to within 10 per cent. (*b*) It gives constant results from year to year. (*c*) It provides a means of detecting the presence of deterioration. (*d*) It is the least affected by adventitious factors. (*e*) It tests the action of the drug upon which its therapeutic use depends. (*f*) It is not too difficult for general use. (*g*) It is neither time-consuming nor too costly. (*h*) By it, widely different preparations can be compared accurately. (*i*) Its results are transferable to man. (*j*) It has the widest range of applicability of all the methods.

Neither the frog nor the guinea pig method fulfils so many of the essential requirements as does the cat method. The cat method fails in no single requisite and has far fewer disadvantages than any other method yet proposed.

Another advantage which the cat method of standardization seems to the writer to possess over the frog method may perhaps be described as psychologic. It is easier to think of dosage in terms of cat units than it is in terms of frog units. Hatcher and Brody quote Focke as saying that he believes it is not feasible to accustom physicians to thinking and calculating the strength of digitalis preparations in frog units. On the other hand, the cat unit strength of the various forms of digitalis is becoming widely accepted. The figures are larger and therefore more nearly approach the therapeutic doses, and they also tend to fall into certain multiples which make them readily applicable for calculations of dosage. Eggleston is of the opinion that the relative toxicity of the various digitalis bodies for the cat corresponds more accurately to the relative potency of these drugs for man than does their toxicity for the frog or guinea pig.

It is very desirable that all forms of digitalis should be biologically assayed by a uniform method, preferably by the cat method for reasons that have been given. The strength of every preparation put upon the market should be indicated preferably in terms of the cat unit, and the date of manufacture and of assay should be stated. In the case of some preparations, and probably in many, the strength of the drug can be adjusted so that a fixed amount has a constant strength. For example, 1 cc. of the tincture should always represent 1 cat unit no matter by whom it is manufactured. This adjustment of strength is very desirable. When this becomes a uniform procedure, the medical profession will learn to use the preparations of digitalis according to their individual potency, and not follow a rule of dosage which may have but little bearing on the preparation being used.

Even though the strength of a preparation of digitalis, as determined by the biological assay method is known, the physician should always study the relation between the amount of the drug given to patients and its effect upon them. He should endeavor to determine the average amount of every preparation that is used necessary to produce well defined digitalis effects. If opportunities are afforded for doing this adequately, as can be obtained in modern hospital practice, perhaps the best method of digitalis standardization for practical purposes is available.

2. The relative potency of the digitalis bodies

The potency of a number of the more important members of the digitalis bodies was determined by Hatcher and Brody (74) and later Hatcher (68) repeated some of this work, correcting a few of the figures reported with Brody. From these two papers the relative potency of these drugs may be tabulated, the number of milligrams of the drug which represents 1 cat unit, or the number of milligrams which is the fatal dose for the cat on the basis of 1 kilogram of body weight of the animal, being used to express their potency.

	mgm.
Ouabain, crystalline	0.10
Strophanthin, amorphous, Boehringer and Sons	0.13
Merck	0.17
Digitoxin, crystalline	0.30 – 0.50
Digitoxin, so called amorphous	1.20
Digitalinum verum, Kiliani	1.50
Adonidin	3.00
Strophanthus, Kombé	3.00
Digitalein	3.50
Digitalin, German	3.60
Digitalis, German	82.00
Digitalis, English	92.00

This table indicates clearly the relative potency of the three active principles of digitalis, digitoxin, digitalin and digitalein, and shows also the relative toxicity of ouabain and amorphous strophanthin.

3. Variations in potency

The varying strength of the preparation of digitalis has been a problem which has caused much uncertainty and discussion. It has confused the question of dosage. The chief sources of the difficulty have been variations in the digitalis content of different specimens of leaves, deterioration and probably variations in absorbability from the gastrointestinal tract. Roth (136) found that in 1916 the methods of biological standardization employed by American drug manufacturers were not uniform and, in some instances, manufacturers were not carrying out a biological standardization of their digitalis products.

Pratt (12) was among the first to show the inefficiency of some of the digitalis on the market. By using the thirty-minute frog method he assayed nine samples of digitalis leaf obtained from leading apothecaries and hospitals in and about Boston, and found only one strong digitalis leaf among the number. A sample obtained from Germany prepared and standardized by Caesar and Loretz proved to be twice as strong as the best leaf obtainable in the American market. Pratt concluded that the available tinctures were also low in potency, as he was unable to obtain the therapeutic results with them which were immediately obtained in the same patients when good powdered leaves were used. Goodall, according to Fulton (56), examined a number of tinctures of digitalis over a period of three years and found

that during this time, nearly half the number had departed from the standard strength, the limit of variation being from 275 per cent over-strength to 40 per cent under-strength. Goodall found that the tincture was apt to deteriorate within a year. The writer found that one lot of the tincture kept in the drug room of a hospital in a 5-gallon container, and which had a cat unit of 1 cc. when first tested, had deteriorated so that the cat unit was approximately 2 cc. at the end of one year.

Roth (136) found by the one-hour frog method a variation of over 250 per cent in the thirteen samples of commercial "fat-free" tincture of digitalis and a variation of 150 per cent in five samples of German commercial digitalis. No definite reason could be given for the initial variations in the samples of the fat-free digitalis.

Newcomb and Rogers (115) who also found differences in the strength of various preparations, consider that the chilling of the tincture of digitalis to a temperature of 40°F., even for a brief period of time, causes an increase in the natural precipitation, which carries down some of the active principles of the drug.

On account of the opinion prevalent among physicians and pharmacists that digitalis and its preparations undergo deterioration with considerable rapidity, Hatcher and Eggleston (76) reviewed this subject and undertook an investigation on the keeping properties of digitalis and some of its preparations. The cat method and, in some instances, the one-hour frog method were employed for estimating the activity of the specimens. They used samples of leaves, ground and unground, tinctures, extracts and fluid extracts ranging from less than one to more than thirty years old. Their findings do not confirm the common belief regarding deterioration, as they found that commercial digitalis leaves of good quality do not undergo any deterioration in many instances as the result of age. In a few cases they do appear to have deteriorated but only with extreme slowness—at a rate probably not exceeding 1.5 to 2 per cent a year. Although the presence of moisture has been emphasized as a cause of deterioration, several of their specimens of leaves had not been protected from moisture. Mouldy leaves, however, must be considered as worthless. Pharmacopial preparations made with a menstruum containing at least 50 per cent alcohol showed no greater deterioration than the

leaves. Of course, the infusion of digitalis is notoriously unstable and those using it carefully usually insist on its preparation within a few days of its administration. Hatcher and Eggleston (77) studied the stability of the infusion, using the same methods employed in their previous work. The most striking facts shown by their experiments are that an infusion of digitalis made without alcohol and kept without the least care, in fact under more unfavorable conditions than should obtain in practice, may retain its activity with little impairment for periods varying from six to nineteen days; and that when the hot infusion is bottled with reasonable care, it will often keep practically unchanged for many weeks even during the summer.

The stability and constancy of the purer substances, such as the single glucosides and especially the crystalline substance such as ouabain would be expected to render them above reproach, from the point of view of stability. But such is not the case. Sollman (142) has pointed out several factors, especially variations in temperature and concentration of the solution which affect the toxic dose of ouabain in frogs, and which may cause errors in the biological assay of the drug. Deterioration of crystalline strophanthin has been found by Levy and Cullen (95) in the preparations marketed for therapeutic purposes. They studied the cause of this deterioration and propose a well founded remedy for it. Many of the glass containers commonly used in the laboratory and most of the glass ampules employed in marketing sterile solutions for hypodermic or intravenous medication yield sufficient alkali on autoclaving to change the reaction of distilled water from pH 6 to pH 9. This increase in alkalinity is sufficient to render biologically inert and practically to decompose aqueous solutions of crystalline strophanthin in the concentration employed in clinical medicine. Levy and Cullen suggest that for clinical use crystalline strophanthin be dissolved in 0.02 M standard phosphate solution at pH 7 and marketed in hard glass ampules, thereby insuring stability of reaction and preservation of the biologic activity of the drug. This work views the question of deterioration of the digitalis bodies from a new angle, from which the deterioration of some of other members of the group should be studied.

The relative potency of the tincture of squill when administered orally as compared with the tincture of digitalis is shown by the recent

work of White, Balboni and Viko (158). They investigated the effect of a standardized tincture of squill on the hearts of a series of patients and found that although squill has a definite digitalis-like action on the heart, it appeared only after doses eight to sixteen times as large as those generally recommended. These observations confirm the opinion of Cushny (30) that, considered clinically, squill has only one-half or one-quarter the effect of digitalis.

The question of absorption from the gastro-intestinal tract is one that complicates the problem of the effects which the various digitalis bodies exert when administered by mouth. As it is not primarily a matter of the relative potency of the various members of the group, it is best discussed after the question of dosage has been taken up.

V. ANIMAL EXPERIMENTATION

The effects of digitalis and its allies on animals have been studied by many investigators and there is an extensive literature on the subject. Those studies in which mammals have been used have furnished the more valuable results from the therapeutic point of view, and some of these studies will be reviewed. These experiments have served as a basis for the analysis of the effects observed in man during the so-called empirical period of the use of digitalis, and they have also pointed the way to the improvement in methods of administration. They have been of great value in rationalizing the therapeutic use of the drug, so that today a fair degree of scientific accuracy is possible in regard to its use. On the other hand, animal experimentation has too strongly dominated the ideas concerning the results to be expected when the drug is administered to patients with heart or circulatory disease.

As Cohn (20) has pointed out, Schmiedeberg and his pupils have emphasized, that the main action of a digitalis body is on the heart muscle; while the school of Gottlieb has been particularly interested in the effects the drug has on the blood vessels, and maintains that it has an important action on the walls of the arteries. "Both schools find that the drug increases the excursion of the heart in contraction, both believe that it elevates blood pressure, both believe that it increases the amount of renal secretion." Recent observations on patients by methods which allow an accuracy closely approaching

that of animal experimentation, make it necessary to readjust our ideas, as the predominating effects on patients on which the beneficial results of the drug depend are not those predicted by animal experiments. The careful clinical observations of Cohn have been of importance in bringing out this point, and he says:

> It is perhaps not an overstatement to say that in a general way clinicians have been too much influenced by these experimental results and have felt obliged to find that the administration of the drug in patients results in parallel phenomena. It requires a very small experience in treating patients suffering from heart disease to find one's self disappointed because the expected results did not occur. And when discrepancies were noticed, the discovery was not often followed by an effort to explain them, the subject was often dismissed by finding fault with the potency of the drug or by discovering an idiosyncrasy in the patient. But even if drugs were always potent and there were no individual idiosyncrasies, it is extremely likely that patients would continue to react in different manners to the drug. And the reason for that must be that individuals, although they suffer from what, in a general sense, is called heart disease, yet present a great variety of clinical pictures.
>
> There can be no question of the usefulness to therapeutics of these experiments; as guides, they are indispensable, but it must be clear that they neither replace nor parallel the clinical conditions we must treat. That there has consequently been a divergence between the results of the pharmacologists and clinicians in a practical sense is inevitable. The responsibility for it is probably shared equally by both. Pharmacologists have dealt usually with simple normal conditions; clinicians with complex pathologic ones.

This review attempts to emphasize the recent careful studies of the effects of digitalis on patients and gives preference to the work from the clinic over that from the laboratory, when the clinical studies are such as to justify this preference. The more exact clinical studies of digitalis were inaugurated by Mackenzie (107) and he was perhaps the first to point out in 1911 that the clinician must exercise great judgment in the application of pharmacological knowledge in the treatment of his patient. The confusion of results from the laboratory and of those from the clinic is caused mainly by the fact that observations have been made on widely different species and that great differ-

ences in dosage have been employed. Uniform criteria have not been employed, and the tissues on which the drug acts have not been exactly ascertained.

The most important statement regarding the question of the value of animal experiments on the therapeutic use of digitalis is that made in 1918 by Cushny (31) one of the foremost experimentalists with digitalis. He said:

> More than a century after the introduction of digitalis, the knowledge of its therapeutic action had made but little progress and was meagre and unsatisfactory, because no accurate knowledge of the clinical action was attainable, and the facts of the laboratory could not be confirmed for man.

Cushny who studied patients with Mackenzie has done much to introduce the new chapter in the study of digitalis, the chapter of exact clinical observations. In his important experimental work, published in 1897, he employed a method which was a forerunner of one of the clinical methods that have thrown much light on the problem of digitalis action. Cushny (28) studied the action of the drug directly on the heart of the dog and observed, by means of the myograph the action of the auricles and ventricles separately, thus making it possible to differentiate the various forms of disturbed cardiac mechanism which have become so important in the clinical study of the drug.

VI. THE NEWER METHODS OF CLINICAL STUDY OF DIGITALIS

The newer methods may be put into two groups. In the first group belong those methods that give accurate information regarding the movements of the various parts of the heart. In the second group, may be put the quantitative clinical methods such as the accurate measurement of the intake and output of fluids, the quantitative estimation of kidney function, the measurement of blood pressure and of the vital capacity of the lungs, together with the variety of useful procedures that have been developed by the application of biochemistry to clinical medicine. All of these methods have been used, not only directly in the study of digitalis in man, but they have also served to differentiate with greatly increased accuracy the many conditions belonging to the general class of heart and circulatory disease, and have so added a degree of specificity to digitalis studies which was hitherto impossible.

The introduction of the polygraph by James Mackenzie inaugurated the methods by which the movements of the auricles and ventricles of man can be studied separately, and by which the efficiency of the mechanism conducting the cardiac impulse from one chamber of the heart to the other can be determined. The value of this method is demonstrated by the masterly studies of digitalis published by Mackenzie (106, 109) in 1905 and 1911 which have added much to our knowledge of the action of the drug in heart disease.

The adaptation of the string galvanometer by Einthoven furnished the second great advance in this direction, and the electrocardiograph has added much to the modern concepts of digitalis action in man. In it we possess a method that not only clearly differentiates all the disturbances of cardiac mechanism, but which also gives us information of importance regarding the direct action of digitalis on the heart muscle, allows the detection of very early toxic effects of the drug on the heart, and serves as an aid in determining pathological conditions of the myocardium.

Although these two methods are not perhaps as yet available to all practicing physicians, the information which they yield is translatable, as Christian (14) remarks "into the terms of general practice, that is, brought into the range of such observations as is possible with fingers, eye and stethoscope."

Of the methods belonging to the second group, comment is necessary perhaps in only one instance, namely the measurement of the vital capacity of the lungs as a means of studying the effect of digitalis. Several years ago, Peabody showed that the vital capacity of the lungs (the amount of air, measured by a spirometer which can be forced from the lungs after the deepest possible inspiration), varied directly with the efficiency of the circulation. He also showed that normal individuals of the same sex, weight and height gave vital capacity readings of sufficient constancy to allow the establishment of a normal standard. West and Pratt (156) have recently reported a series of cases to which digitalis was administered and in which the vital capacity of the lungs was taken as one of the criteria for the estimation of the effect of the drug. Although it is not entirely clear how the improvement of the circulation causes an increase in the vital capacity, the method holds promise as a means of estimating quantita-

tively the functional efficiency of the circulation, and may therefore fulfill, at least in part, one of the greatest needs in the study of the effect of digitalis in heart disease. This method, the technique of which is quite simple, should be included in all comprehensive studies of the effects of digitalis on man.

VII. THE TOXIC EFFECTS OF DIGITALIS

In considering the effects of digitalis on man, they are naturally separated into those that are advantageous and those that are deleterious, especially to patients suffering from heart and circulatory disturbances. These two groups of effects may be spoken of as the therapeutic and the toxic effects. In most instances, the two groups can be separated by the ultimate results of each on the circulation as a whole, but sometimes the prevailing conditions of the circulation may make this separation somewhat difficult, as effects which would be considered toxic, under most circumstances, may have, under some conditions, therapeutic value. Therapeutic and toxic effects may also occur simultaneously when the drug is being administered in large doses to patients, and the close relation between the optimum therapeutic dose and that producing early toxic symptoms presents one of the greatest problems involved in the skilful use of the drug in therapeutics. For instance, Bailey (quoted by Bastedo (5)) found that of ninety patients in Bellevue Hospital taking digitalis, about 25 per cent showed one or more toxic effects of the drug.

The characteristic effects of all members of the digitalis group are those on the heart and on the central nervous system, but in order to understand the action of these drugs so that they may be intelligently employed in the treatment of disease, a close analysis of their effects must be made and careful consideration must be given to the various pathological conditions they may be expected to benefit.

The first requisite for the successful employment of digitalis as a remedy is the recognition of its toxic effect, especially of those early effects which serve as indications for the discontinuance of the drug. For this reason the deleterious or toxic effects of the drug will first be discussed.

1. Gastric effects

In the earliest accounts of digitalis, reviewed by Withering (163), the effects of the drug on the gastro-intestinal tract were described, and it was spoken of as a poison having an emetic and a purgative action. All modern study of digitalis has taken into account the gastric symptoms, loss of appetite, nausea and vomiting which constantly follow the use of all members of the digitalis group in large doses; and they have been recognized as among the earliest toxic symptoms which the drug produces.

Anorexia, nausea and vomiting are symptoms observed by all who have used digitalis in sufficient doses, as they are probably the commonest of the "side-actions" as Eggleston puts it, encountered in the clinical use of the digitalis bodies.

The peculiarities of the emetic action of digitalis were noted by Withering (163) who wrote:

> It is curious to observe that the sickness, with a certain dose of this medicine, does not take place for many hours after its exhibition has been discontinued. . . . . The sickness then excited is extremely different from that excited by any other medicine; it is peculiarly distressing to the patient; it ceases, it recurs again as violent as before; and then it will continue to recur three or four days at distant and more distant intervals.

Vomiting should be avoided if possible, especially when digitalis is being given to patients with severe symptoms of heart failure. This is an important reason for the recognition of the earliest toxic effects of the drug, in order that it may be stopped before the onset of vomiting. As Pratt (122) says,

> Vomiting may be preceded by a day or two of complete anorexia, which should be a sign for the immediate discontinuance of the drug, when it seems evident that the anorexia is caused by the digitalis. It is then an indication that the so-called physiologic limit has been reached, and that nausea and vomiting will follow if more digitalis is given. The stoppage of the drug at the first appearance of anorexia does not always prevent vomiting, but it does not, as a rule, last more than a few hours under these conditions. When the drug is administered until vomiting actually occurs, nausea and vomiting may be present for two or three days and occasionally for a week, passing off and recurring several times, even after the drug has been stopped, as Withering observed.

A difficulty in avoiding nausea and vomiting during digitalis administration is the fact that in some cases, the desired effects of the drug on the heart are obtained with the same dose as that producing the gastric symptoms. Mackenzie (107) noted in his cases that the cardiac effects usually preceded the gastric symptoms, but the two occurred synchronously at times, and Cushny (30) states that minor toxic symptoms, loss of appetite, headache, nausea and vomiting and often diarrhoea usually accompanied the improvement of the circulation produced by the drug. Clinical judgment is the only guide in dealing with individual cases which present this dilemma. Confusion sometimes arises in patients whose stomachs are in a highly irritable state, as is not infrequently seen in heart failure, and who vomit when anything is taken into the stomach. Such patients will often vomit within a few minutes after a dose of digitalis, and then it is safe to say that the drug is not responsible for the vomiting. The reason for this statement will become evident when the mechanism of the emetic action of the digitalis is discussed. Such vomiting should not be taken as a sign for the discontinuance of the drug, as the gastric symptoms may disappear with an improvement of the circulation. A method of administration other than oral may have to be resorted to, however, in such cases.

The relation of the therapeutic use of digitalis to nausea and vomiting has been studied by Eggleston (40) in a series of 15 patients, all of whom were suffering from heart disease. Digitalis was given in the form of the infusion or tincture in the usual or slightly larger doses, as a rule, every four hours. Eleven cases were instances of auricular fibrillation. In this series nausea alone, or nausea and vomiting developed on an average of five days from the beginning of the digitalis administration, when an average of 3.08 grams, corresponding to $7\frac{3}{4}$ drams of the tincture had been taken. In the 4 cases with regular cardiac rhythm, nausea or vomiting occurred in seven days, after the average dose of 2.4 grams of the drug had been given. The average dose in these cases was smaller than that given to the patients with auricular fibrillation. In none of the 15 cases did the onset of nausea or vomiting bear any constant time relation to the administration of the individual doses of the drug. In most cases nausea or vomiting persisted or recurred for some hours after the last dose had been given and the drug withdrawn.

In estimating the total amount of digitalis which will, on an average, lead to nausea and vomiting, the question of elimination of the drug during the days of its administration must be taken into account, and only rough estimates can be made which have any value when applied generally to patients. Large single doses of digitalis were administered to about 100 patients by Robinson (130), the doses usually ranging from 15 cc. to 25 cc. of a standardized tincture, or 1.5 to 2.5 gram of digitalis. The patients were all adults, and suffered from a variety of cardiac disorders. Only about 10 per cent of these patients showed the toxic gastric symptoms caused by digitalis. Nausea and vomiting came on in these cases in from one-half to one hour after the large doses had been given. Eggleston (40) has collected and tabulated 95 cases from the literature to which digitalis bodies were given in the usual doses until nausea or vomiting appeared. The cases of this series were divided into three groups. The first consisted of cases of auricular fibrillation, the second group of non-fibrillating cases and the third group receiving digitalis bodies other than the leaf. In reviewing the first two groups, it is seen that the dose of digitalis producing nausea or vomiting varies from 1.25 grams to 8.50 grams and the figures are not sufficiently constant to warrant an average of significance to be obtained from them. The dosage falls, however, most often between 2.5 grams and 3.5 grams. A comparison of these two groups of cases leads to the conclusion that the type of heart disease has no direct influence on the amount of digitalis required to produce gastric symptoms, which occur also with approximately the same doses in individuals with normal hearts. The analysis of cases of the third group shows that crystalline digitoxin (Nativelle's digitalin granules), tincture of strophanthus and of squills, and the extract of apocynum also cause nausea and vomiting, when given in sufficient doses. Cushny (30) concluded from clinical observations that digitalis had perhaps less effect on the gastrointestinal tract than strophanthus and squills.

The mechanism by which the digitalis bodies produce their emetic action has been only recently clearly demonstrated, although much speculation and some experimentation had been carried on regarding it. In 1912, Hatcher and Eggleston (75) pointed out that the emetic action of the drug had been generally attributed to its irritant action

on the gastric mucosa, but that there were several discrepancies between the deductions which had been drawn from animal experiments and the occurrence of nausea and vomiting in patients receiving therapeutic doses of the drug. They observed that the digitalis bodies, as a rule, produced emesis more rapidly and with smaller doses when given intravenously than when introduced into the stomach. In order to eliminate the possibility of action of the drugs during excretion from the blood stream into the stomach, digitalis and several of its allies were injected intravenously into dogs from which the gastro-intestinal tract had been removed. Sixteen of the 21 eviscerated animals went through the motions of vomiting, after the injection of these drugs, and three others showed signs of severe nausea. They injected digitalis, digitoxin, true digitalin, ouabain, strophanthus, amorphous strophanthin and adonis. Hatcher and Eggleston conclude from their experiments that the emetic action of these drugs is exerted upon the vomiting centre in the medulla and is not caused by the local irritation of the gastric mucosa. They consider the purgative action also as obviously of central origin.

Just as this review is going to press, the report of Hatcher and Weiss (78 a) on the emetic action of the digitalis bodies has appeared in a preliminary form. They state that Thumas has shown that the direct application of the digitalis bodies to the vomiting centre in the medulla does not cause emesis. By means of a series of experiments on cats in which various nervous structures were cut, Hatcher and Weiss have shown that digitalis causes emesis only when the nerve supply to the heart is intact. The vomiting centre is not stimulated directly, but by impulses reaching it from the heart, passing up by way of the sympathetic, and to a less, though probably variable extent, by way of the vagus. Ouabain usually failed to produce vomiting after the sympathetic only was cut.

These investigators consider their experiments as evidence that the digitalis bodies induce emesis by reflex action due to irritation of the heart or its appendages. The effect they consider as almost certainly a protective mechanism for the heart such as is recognized in the case of other organs. With the establishment of the fact that emesis is not an effect produced by the direct action of digitalis on certain structures of the medulla, but is secondary to the direct

action of the drug on the heart, a new attitude must be taken regarding its relation to the cardiac effect of the drug. The effect of the drug on the heart and its effect in producing nausea and vomiting cannot be dissociated and the latter would seem to have a more significant place than has been given to it in evaluating the cardiac action of digitalis.

In a second paper Eggleston and Hatcher (48) investigated the relative emetic activity of a number of more commonly used digitalis bodies and also of several proprietary preparations for which diminished emetic action was claimed. They determined the percentage of the fatal dose required to produce emesis in cats when injected intravenously. The minimal dose and the average of the emetic doses of various digitalis bodies and specialties in percentage of the minimal lethal dose of each drug are given in their paper as follows:

DRUG OR SPECIALTY	EMETIC DOSE IN PERCENTAGE OF FATAL DOSE	
	Minimal	Average
True digitalin	18	22
Strophanthus	27	47
Ouabain	30	49
Digitalis	31	46
Crystalline digitoxin	40	58
Amorphous strophanthin	61	65
Digipuratum	25	42
Fat-free tincture of digitalis	28	34
Digitalysatum	29	36.5
Digalen tablets	29	40
Digalen, liquid	30	38

Eggleston and Hatcher have shown therefore that all these digitalis bodies and preparations have an emetic action which do not differ quantitatively very markedly. True digitalin is the most active emetic, while amorphus strophanthin and digitoxin are the least active in percentage of their fatal doses. There is very little difference between digitalis and various specialties, and these experiments furnish no evidence that digalen, digipuratum, digitalysatum and the fat free tinctures have any advantage over the less expensive galenical preparations of digitalis from the point of view of being

less disturbing to the stomach when used therapeutically. These authors conclude that there is at present no means of securing the cardiac action of the digitalis bodies without subjecting the vomiting centre to the influence of these agents at the same time, and there is no advantage in substituting one mode of administration, or one member of a group for another, in an attempt to prevent or lessen the gastric symptoms which these drugs cause. They also express their disapproval of the employment of opium as has been advocated to prevent the gastric symptoms, as it may serve to mask the toxic symptoms which should serve as a signal for the discontinuance of the drug or the reduction of the dose.

These experimental studies were followed by the clinical study of Eggleston (40) to which reference has already been made, and in which he correlated clinical experience with the facts of the experiments. He showed in his own series of 15 cases and in 95 cases from the literature, nausea and vomiting almost never occur as a result of digitalis until it had been absorbed sufficiently to produce its characteristic effect on the heart. His study shows that there is no valid evidence that therapeutic doses of the digitalis bodies cause nausea or vomiting through local irritation on the alimentary tract, but that there is strong evidence to the contrary. He concludes, therefore, that the nausea and vomiting resulting from the therapeutic use of digitalis and its allies in man are due to their direct action on the vomiting center in the medulla. Eggleston draws the deduction from his conclusions that preparations which fail to produce nausea and vomiting when administered in large doses are either weaker than those that do produce these effects or are less well absorbed.

Vomiting may be considered as a desirable effect from one point of view, as it may prevent further toxic symptoms from following an overdose of the drug when taken by mouth, as part of the drug may be eliminated when the stomach is emptied by the vomiting which it produces.

The purgative action of digitalis has not been prominently described in recent clinical studies, and its absence was noted in the 42 patients carefully studied by Mackenzie (107) to whom sufficient digitalis was given so that gastric symptoms usually occurred. He found,

however, that diarrhoea was produced by strophanthus and squills. Bastedo (5) also noted that diarrhea is much less frequent than anorexia, nausea and vomiting as a sign of overdose in digitalis administration. The writer's experience confirms these statements.

2. Toxic effects on the heart

Although the gastric disturbances are the most obvious unfavorable effects of digitalis, the cardiac disturbances must be regarded as the most serious in the clinical use of the drug. It is the direct effect of digitalis on the heart which produces death in animals to which a lethal dose is administered, and certain disturbances of the heart-beat resulting from an overdose of the drug to man must always be considered as the forerunner of effects which profoundly lower the efficiency of the circulation and which render the heart eventually incapable of maintaining the circulation. For this reason, the early recognition of the unfavorable effects of the drug on the heart is a matter of paramount importance.

When Cushny (28) first studied the effect of digitalis on dogs by a method that allowed the activity of auricles and of ventricles to be distinguished in graphic records, he discovered early effects which he attributed to the stimulating action of the drug on the vagus centre and later effects which he considered as the result of the direct action of the digitalis on the heart muscle. These later effects, constituting the second stage of digitalis action, were attributed mainly to an increase in the irritability of the myocardium.

Robinson and Wilson (134) administered digitalis intravenously to cats and followed the effect of the drug on the heart by electrocardiograms. It was found that when about 75 per cent of the lethal dose was administered, evidence of increased irritability of the ventricles appeared, manifesting itself as premature contractions which were soon followed by idioventricular rhythm, when cardiac impulses were being generated at a more rapid rate in the ventricles than in the auricles. This state of affairs was followed, during further administration of the drug, by ventricular fibrillation and death.

More recently Levine and Cunningham (94) using the same methods have found that when various preparations of digitalis were injected

into cats, premature ventricular contractions or extrasystoles appeared when an average of 48 per cent of the lethal dose was administered, and they considered the appearance of this phenomenon to mark the onset of increased ventricular irritability. They used the appearance of ventricular extrasystoles therefore as evidence of the first toxic sign of digitalis.

The analysis of unfavorable effects of the drug on the heart when administered to man had its inception with the first of Mackenzie's studies published in 1905, when he described the bigeminal pulse and recognized that its production resulted from frequent ventricular extrasystoles. He also showed that the conduction of the cardiac impulse is disturbed by the drug. In 1911, Mackenzie pointed out that digitalis may cause irregularities of impulse production, extrasystoles, partial heart-block, and pulsus alternans. The cardiac manifestations of overdose in digitalis administration were studied by Bastedo (5) who made polygraphic records of patients receiving the drug, and demonstrated the occurrence of auricular and ventricular extrasystoles, partial heart-block, paroxysmal trachycardia and possibly pulsus alternans. Bastedo recommends that digitalis be discontinued whenever the radial impulse rate goes below 60 per minute, whenever sudden slowing of the heart rate indicates the occurrence of heart block, whenever a regular ventricular rhythm becomes irregular, whenever tachycardia occurs or whenever coupled rhythm or phasic arrythmia appear in hearts showing auricular fibrillation.

a. Premature contractions. The two outstanding disturbances of the cardiac mechanism which digitalis causes in patients are those resulting from increased irritability of the ventricles and from depression of the conduction of the cardiac impulse from auricles to ventricles. The effect of digitalis on the ventricles leads to the occurrence of *premature contractions* of ventricular origin, commonly called extrasystoles. They are, generally speaking, always detrimental to the efficiency of the heart. Premature ventricular contractions tend to occur in diseased hearts and are, in many patients needing digitalis, readily provoked by relatively small doses of the drug. They appear to be provoked especially readily in patients with auricular fibrillation, when coupled rhythm replaces the absolutely

irregular cardiac action. At times these premature beats occur so frequently after small amounts of digitalis that it is the better part of judgment to discontinue or diminish its use before the optimum therapeutic effects are obtained.

The occurrence of ventricular premature beats may be readily recognized by the stethoscope with the finger on the pulse when they occur in hearts beating otherwise regularly. Except when definite coupled beats occur, it is impossible to recognize premature ventricular contractions however in cases of auricular fibrillation without electrocardiograms, which alone show, by the variations in form of the ventricular complexes, that some of the cardiac contractions are arising from ectopic points in the ventricles. The frequent occurrence of ectopic ventricular contractions during the use of digitalis in auricular fibrillation may be sometimes responsible for the failure to get the ventricular slowing that the drug usually produces in these cases.

There is a great difference in patients as to the amount of the drug which causes the onset of premature ventricular contractions, and no statement as to the average amount required can be made. It is evident, however, that in many patients ventricular contractions occur with an amount of the drug which is a much smaller proportion of the lethal dose than has been observed during the intravenous administration of the drug to cats.

Edens and Huber (38) have discussed the production of premature ventricular contractions by digitalis, and the occurrence of the bigeminal pulse. They consider it probable that the bigeminal pulse follows the administration of digitalis only in hypertrophied hearts with lowered muscular efficiency. They believe that the production of the bigeminal pulse by digitalis is an unfavorable prognostic sign. They also point out the great variability in the size of the dose which brings about the bigeminal pulse. Although their ideas regarding the relation of cardiac hypertrophy and inefficiency to the digitalis bigeminal pulse have not been confirmed, it is a point worthy of close attention.

The frequency of apparently spontaneous premature beats may lead to some difficulty in fixing the responsibility for them during digitalis administration, but it should be emphasized that it is a

definitely established fact that they may be caused directly by digitalis, and should always be considered as a probable toxic effect whenever they occur during the administration of any member of the digitalis group. The influence of digitalis on apparently spontaneous premature contractions will be discussed later.

The production of the so-called auriculo-ventricular rhythm by digitalis is an effect of the drug closely related to the production of premature ventricular contractions. This type of disturbed cardiac mechanism has been observed by Cohn (20) to follow the administration of digitalis and to disappear when digitalis had been completely eliminated. In auriculo-ventricular rhythm, the auricles and ventricles beat independently but each at nearly equal rates. Electrocardiograms indicate that the auricular stimulation is not usually disturbed, while the auriculo-ventricular node (of Tawara) assumes the rôle of ventricular pace-maker, by generating stimuli at a slightly faster rate than the sino-auricular node. Auriculo-ventricular rhythm is associated only with various forms of cardiac intoxicants, notably digitalis.

b. Depression of conduction of the cardiac impulse from auricles to ventricles is one of the most striking effects of digitalis, which may lead to partial or complete heart-block. This action of the drug is generally considered to result, for the most part, from its stimulating effect on the cardio-inhibitory mechanism, although there is not entire agreement as to the relation of this effect to the direct action of the drug on the cardiac tissues.

The great value of digitalis in certain forms of heart disease depends largely upon its ability to block impulses in their passage from auricles to ventricles, and for this reason the action of digitalis on conduction will be discussed when the therapeutic effects of the drug are considered. On the other hand, heart-block produced by the administration of digitalis may definitely lower the efficiency of the circulation and it must be considered therefore as a toxic manifestation of the drug. Its recognition and the means of avoiding its production will be briefly discussed at this time.

Mackenzie (106) first demonstrated heart-block as an effect of digitalis in man in 1905. Since that time, the influence of digitalis on conduction has been extensively studied by graphic methods.

As Bastedo (5) has pointed out, when a rapidly beating heart becomes suddenly slowed during the administration of the drug or if an intermittent cardiac rhythm unassociated with premature beats develops, it is safe to infer that heart-block exists. These events should be taken as indications for discontinuing the administration of digitalis.

Uncertainty of the diagnosis of heart-block will always exist, however, without the employment of the polygraph or the electrocardiograph. It is only by these methods that the earlier effects of digitalis on conduction, when the cardiac impulses are merely delayed in their passage from auricles to ventricles, can be detected. It is distinctly advantageous, therefore, to employ these methods during the administration of digitalis in order to detect its effect on conduction before a stage is reached which may lower the efficiency of the heart.

A number of students of digitalis, among whom are Edens (37) and Cushny (29) have expressed the opinion that digitalis affects especially the conducting system of heart in which auriculo-ventricular conduction has been previously damaged by disease. Although Cohn and Fraser (22) have shown that this is by no means a necessary condition for the production of digitalis heart-block, it must be a predisposing factor in some instances. It is very desirable to know the functional state of the conducting system before the administration of the drug to patients with heart disease, and this information is furnished by measuring the time between the onset of auricular activity and ventricular activity. When this time is found delayed beyond the normal limits, it should be taken as a contraindication for the use of digitalis or it should call for caution, careful observation, and alteration of dosage.

R. H. Halsey (64) has reported a case showing profound effects brought on apparently by excessive vagus stimulation producing severe subjective symptoms. Following the administration of digitalis to a patient with auricular fibrillation, severe cardiac failure and Cheyne-Stokes breathing, marked variation in the ventricular rate from 100 to 50 beats per minute were observed, the rapid rate occurring during the periods of apnea. This phenomenon apparently interfered with the interchange of O_2 and CO_2, and was relieved by atropin when the ventricular rate became 150 per minute.

Windle (161) studied the comparative effects of digitalis, strophanthus, squill and apocynum on the conduction of cardiac impulses in a case of mitral stenosis which required treatment on four occasions. He used a different drug each time, the tincture of each being employed. Apocynum had no effect on conduction, while the other three drugs caused partial heart-block with approximately equal amounts.

> 630 minims of the tincture of digitalis were given in 14 days
> 540 minims of the tincture of strophanthus were given in 19 days
> 480 minims of the tincture of squill were given in 4 days.

When heart-block was observed in each instance it is evident that these three members of the digitalis group required total amounts which are comparable to produce partial heart-block in this case, although the rate of administration was different.

c. Other disturbances of the heart beat have been observed occasionally following large doses of digitalis. The auricles are affected, although less frequently, in the same manner as the ventricles, and premature auricular beats sometimes occur during the digitalis administration, presumably as a result of the action of the drug. Bastedo (5) has reported a case of paroxysmal tachycardia which he considered as produced by digitalis, but the relation of the inception of this disturbed cardiac mechanism and the action of the drug seems uncertain.

Special interest is attached to the influence digitalis may have in causing auricular fibrillation. Cushny (30) has stated that digitalis may cause the onset of auricular fibrillation and Danielopolu (33) has reported three cases in which auricular fibrillation followed the administration of the drug, in each instance the onset of fibrillation occurring coincidently with the maximum digitalis action. Danielopolu considered that in his cases the auricles were predisposed to fibrillation which was provoked by the stimulating effect of the drug on the vagus. Mackenzie (107) has reported a case in which auricular fibrillation set in at the time when an amount of digitalis sufficient to cause maximal effects had been given, and disappeared four days after the discontinuance of the drug. Robinson (126) studied a case of paroxysmal auricular fibrillation to whom digitalis was administered, but was unable to draw any definite conclusion

as to the influence of the drug on the persistence of the fibrillation. Agassiz (2) administered strophanthin intravenously to such a case, with the result of apparently prolonging the paroxysm of auricular fibrillation, although the ventricular rate was slowed by the drug. It is these cases of transient auricular fibrillation in which the question of the relation of the drug to the production of this cardiac disturbance is especially important. The evidence seems sufficient, as Fulton (56) points out, to warrant the conclusion that digitalis does predispose the auricles to fibrillation, and its use may therefore be disadvantageous in cases where it is desirable to prevent recurrent attacks of fibrillation, or where a cessation of fibrillation may be expected, although the drug may be very useful when fibrillation is present. Clinical judgment can be the only guide under such conditions.

Auricular standstill has been observed by White (157) as an effect of digitalis in cases of heart disease. In these cases, both electrocardiograms and graphic records from the jugular vein failed to show any evidence of auricular activity during the height of digitalis action. In all three cases, the auricular activity returned when the effects of the drug passed off. White considers this phenomenon as a rare result of digitalis administration, and no other similar cases are to be found in the literature. Atropin was administered in one case, but had no effect upon the cardiac mechanism except for a slight increase of rate.

White and Sattler (160) have also described a curious arrhythmia consisting of blocked auricular premature beats occurring in a healthy subject after 3 grams of digitalis had been taken. *Sinus arrhythmia* in which the rhythm of impulse formation is disturbed, is commonly observed with large doses of digitalis, as first pointed out by Wenckebach (155). A number of cases of *sino-auricular block* produced by digitalis have also been observed by the electrocardiographic method, as a result of digitalis action.

Pulsus alternans, a condition in which the regularly beating ventricles contract with alternating force, is generally considered a sign of disturbed contractility of the heart muscle, and of serious prognostic significance. Mackenzie (107) and Windle (162) each state that they have observed this phenomenon as a sequel of digitalis administration in two cases. Bastedo (5) reports one case

which he considered as possibly pulsus alternans produced by digitalis, but his records do not allow him to make a definite diagnosis, and his published curves are not characteristic of this condition. These cases are important as an indication that digitalis may affect the heart muscle, presumably directly, in such a way as to lower its efficiency. Bastedo believes that pulsus alternans results from a constriction of the coronary arteries produced by digitalis, but this idea must be considered purely hypothetical, as there are no definite facts to support it.

Weil (154) has brought forward a criterion for the early recognition of digitalis intoxication which is somewhat different from those that have already been mentioned. He has shown that, under the influence of the drug, the heart becomes more responsive to pressure over the vagus nerves in the neck, and he believes that a well marked vagus response during digitalis administration in a heart which was previously less responsive may be used as indicating the onset of toxic digitalis effects.

3. Fatalities resulting from digitalis bodies.

It is not within the scope of this review to discuss fatalities resulting from amounts of digitalis far in excess of those used for therapeutic purposes. According to Sollmann (143) 2.5 grams of digitalis have proved fatal when taken at one dose, while 4 grams have been followed by recovery. Sollmann states that the symptoms of a fatal dose are those of "cumulation"—gastro-intestinal disturbances, slow and arrhythmic pulse, etc., lassitude, muscular weakness and sensory derangement. Death generally occurs suddenly, with dyspneic convulsions. Consciousness persists late.

Sudden death has been seen occasionally following the administration of the drug in the treatment of heart disease, and fatalities occurring under these conditions must be considered as possibly caused by the drug. During the administration of digitalis by mouth in the usual doses, it is difficult to say what rôle the drug might play as a cause of sudden death. Since the introduction of the intravenous method of administration, however, fatalities have apparently resulted from the injection of the digitalis bodies into a vein. These have most often followed the use of strophanthin, and according to inquiries made by

the writer, have been seen more often than the literature would make one believe. Bastedo (5) remarks that he has heard of one death following the intravenous injection of digitalis in a man and of several such fatalities occurring in from three minutes to an hour after the injection of strophanthin. The writer has observed 1 case in which death occurred suddenly about five minutes after 1 mgm. of strophanthin was given intravenously, and at least 3 other such cases have been related to him by others. Recently Rahn (123a) has reported 2 fatalities following intravenous injections of strophanthin and has reviewed 16 other cases collected from the literature in which death occurred in such close connection with the intravenous injection of the drug as to make a relation of cause and effect seem very likely. In 11 of the cases the causal relation seems certain. Rahn discusses the clinical significance of these deaths and is of the opinion that some of these could have been avoided by smaller doses, longer intervals between doses and a better knowledge of previous administration of digitalis. He believes that the drug should be given by this method only after careful study of the patient. The sudden fatal termination and the relatively short interval between the injection and death seen in a number of these cases leads to the conclusion that strophanthin caused the ventricles to fibrillate, a cardiac state incompatible with life. Ventricular fibrillation is the final stage of cardiac intoxication in most cases when the digitalis bodies are injected intravenously into cats, as shown by Robinson and Wilson (134) and by Levine (92). It is likely that the fatal cases under discussion occurred in patients in whom cardiac damage had already rendered the ventricles prone to fibrillation.

Garrey (57) has investigated the underlying factors responsible for fibrillation of the cardiac muscle, and has advanced an explanation of this phenomenon on the basis of his experiments. The essential points in Garrey's conception of fibrillation are these. Fibrillary contractions of the heart muscle depend upon the establishment within the musculature of multiple regions of block or impaired conductivity. The impulses thus blocked or delayed take abnormal or circuitous paths, and return to the same portion of the muscle after the refractory state has passed off, but while other portions are still refractory. The latter portions are subsequently involved in a

similar manner, and the whole tissue mass is then thrown into a continuous incoördinated contraction, which is not initiated or sustained by new impulses arising from any definite location.

With these points in mind it seems reasonable to consider evidence of impaired conduction within the ventricles as a contraindication to the intravenous use of full doses of strophanthin or other digitalis bodies. Such evidence is sometimes obtained by the study of electrocardiograms, as certain abnormalities in the form of the ventricular complexes indicate delay or abnormal conduction routes in the ventricles. The bearing of these abnormal complexes to the administration of strophanthin has been discussed by Robinson and Bredeck (131), who express the opinion that such electrocardiographic findings should be taken as a contraindication to the intravenous use of strophanthin, and they show the relation these abnormal electrocardiograms may have to ventricular fibrillation.

Although the danger entailed in the intravenous administration of strophanthin has been generally recognized, other digitalis bodies have not received as much consideration from this point of view. Levine and Cunningham (94) however have studied the so-called margin of safety of intravenous digitalis administration in cats, and draw certain conclusions from their experiments bearing on the intravenous use of the drug. They determined the percentage of the lethal dose which produced the earliest demonstrable toxic signs. The minimal toxic dose was calculated in their experiments as the smallest dose that is required to produce ventricular extrasystoles, demonstrable by electrocardiograms. The margin of safety was taken as the difference between the minimal lethal dose and the minimal toxic dose. They have introduced

> the concept of the margin of safety of digitalis preparations because, in the practical use of the drug, the therapeutic dose is very close to the toxic dose. Therefore, it is of great importance to know how far removed the lethal dose is from the toxic dose, and whether the margin is greater in some preparations than in others.

They used aqueous extracts of several different samples of leaves, several different tinctures, and ampoules of Digifoline, Digalen and Digipuratum. They found considerable variations in different

animals both in susceptibility to the drug and in the margin of safety which varied from 27 to 64 per cent. The average margin of safety, however (the difference between the percentage causing death and that causing earliest evidence of toxicity), was 48 per cent of the lethal dose. This difference is identical with the results which Levine (92) obtained in previous work with crystalline strophanthin or ouabain. Levine and Cunningham (94) state on the basis of their findings that

> the practical consideration that follows from these experiments is that although the various digitalis bodies, when given by mouth, are generally regarded as much safer than intravenous administration of strophanthin, when the entire digitalis glucosides (either the aqueous or the alcoholic extracts) are given intravenously, the same risk is encountered as in using strophantin.

They found also but little difference in the rapidity with which the various digitalis bodies and crystalline strophanthin act on the heart when introduced directly into the circulation.

If these experiments can be applied to man, and it seems only safe to assume that they can, it must be borne in mind that the risk of introducing digitalis directly into a vein appears to be as great as when strophanthin is used.

The question of the percentage of the lethal dose which is employed in the treatment of heart disease has been discussed by Robinson and Wilson (134) in the light of their experiments in which the tincture of digitalis was administered intravenously to cats. They consider the inversion of the T wave of the electrocardiogram the digitalis effect offering the most useful comparison of the effects of the drug on the cat's heart and the effects obtained in man. The T wave became inverted in their experiments when from 20 to 30 per cent of the lethal dose had been injected. The maximum therapeutic effects of digitalis usually occur with a dose not much in excess of the amount sufficient to cause inversion of the T wave. Robinson and Wilson, taking these facts into consideration, have expressed as their opinion that the maximum therapeutic effects are probably produced in man by the administration of from 30 to 40 per cent at most of the lethal dose of the drug.

VIII. THE THERAPEUTIC EFFECTS

The beneficial effects exerted by the digitalis bodies upon patients suffering from heart disease are dependent, not upon a single mode of action of the drug on a single organ, but upon a combination of effects. The relative importance of the various activities of digitalis in its therapeutic use has been the subject of much controversy for many years, and although much of this controversy has been cleared up, several points remain about which there is no unanimity of opinion. As has been stated, animal experimentation has added confusion, in some respects, to the problem of determining how digitalis benefits patients with heart disease, and the question can receive its final answer only by the study of patients.

The various effects which may enter into the therapeutic action of digitalis will be discussed separately and their relative importance will be considered in connection with the use of the drug in various forms of heart disease.

1. The effect on the heart muscle.

a. The effect on ventricular contraction. The relation of the effect of digitalis on ventricular contractions to its beneficial influence in heart disease has been much discussed, but this problem has not yet been definitely solved. Its solution is difficult, partly because there has been no certain means of measuring the direct influence of the drug on the efficiency of the heart muscle, and partly because the various factors entering into the therapeutic action of the drug cannot be sharply differentiated from one another. In spite of the uncertainty which actually exists, digitalis has been generally considered for many years as a so-called "heart tonic," and its beneficial effect has been considered as mainly due to an increased output of the heart by its action on the muscle itself.

The older conception is well illustrated by a statement made by Balfour in his clinical lectures on Disease of the Heart, quoted by Schmoll (141).

> All the benefits we obtain from digitalis are inseparably connected with its tonic action; they flow from the power that digitalis has of increasing muscular activity, and the improved metabolism of all the tissues, but especially of the myocardium.

Schmoll expresses his belief that the drug acts as a specific by its effect on the tonicity of the heart muscle.

Schmiedeberg (140) basing his opinion apparently on the results of animal experiments states in the seventh edition of his text book, that the therapeutic action of digitalis is due almost exclusively to its effect on the heart muscle. He considers an increase in the elasticity of the heart muscle the most important effect of the drug and that the change in elasticity is also responsible for the systolic standstill of the heart produced by the drug. Schmiedeberg believes that all other effects of digitalis are mainly secondary to the increased force of the cardiac contractions which the drug calls forth.

Other students of the effects of digitalis on animals, notably Cushny, have found that the drug causes an increase in the output of the mammalian heart under experimental conditions, which occurs in excess of that which results from the slowing of the heart rate alone.

Another experimental pharmacologist Gottlieb (59) states that the work of a single contraction of the isolated mammalian heart may increase under the influence of digitalis two and a half to three times, and Gottlieb summarizes his conception of the therapeutic action of digitalis as due principally to more complete contraction of the ventricles and re-distribution of the blood in the vessels. He believes the drug may strengthen the contractions of the "weakened heart."

It does not seem profitable to enter into a discussion of the experimental studies of this subject, as the conditions under which facts have been adduced are not applicable to a consideration of the therapeutic action of digitalis. In this connection, Cohn (20) has said

> Those effects reported earlier, of changes in the magnitude of ventricular contractions gained in experiments, are more recently admitted (Joseph) to have been obtained by doses far too great. The much smaller doses now used are still much larger than are permitted in therapeutics, but even these fail to show marked changes in the extent of the excursion of the ventricular wall which was formerly held to indicate the nature of effective digitalization. The methods employed in pharmacology are not superior to those now available in clinical medicine. Both are on a par in respect to obtaining objective records of this phase of digitalis action.

In the absence of accurate means of measuring the therapeutic action on the heart muscle, the opinion of various clinical investigators must be considered more as impressions than as well founded convictions. In Mackenzie's (106) first studies on digitalis, he says that the good effect on the cardiac contractions may be due to the slowing of the cardiac rate, but under certain circumstances, the fact that digitalis may effect the function of contractability directly can be demonstrated in a most striking and convincing manner. In his later clinical studies, however, when he was in possession of a more extensive knowledge of the cardiac mechanism and its derangements, he stated that he was unable to determine that the drug affected the heart muscle, but admits that changes may take place in the heart which we cannot detect.

Wenckebach (155) believes that digitalis increases the strength of the human heart by its direct action on the heart muscle, but that there is no evidence that the drug acts on the obscure property, tone of the muscle. Edens (37) has advanced the hypothesis that the poor nutritional condition of the myocardium which is presumably present in heart disease tends to prevent digitalis from exerting its effort on the cardiac contractions, and offers this explanation for his inability to observe any direct action on the heart muscle. Cohn (20) in speaking of the effects of the drug when administered to patients in doses calculated to produce the optimum effects in heart disease stated in 1915, "that if digitalis increases the ability of the ventricles to pump blood, it does so by means of a change which is more subtle than can be distinguished by our methods."

With this limitation of the knowledge regarding this important factor in explaining the action of digitalis in mind, Cohn and Levy (26) have undertaken an investigation of the effect of therapeutic doses of digitalis on the contraction of heart muscle by means of animal experiments. They have been careful to use doses of the drug which were comparable in percentage of the lethal dose to those administered to patients. The tincture of digitalis and g-strophanthin were injected intravenously into dogs and cats, and alterations in volume output were studied in curves obtained by the use of the Roy and Adami myocardiograph.

The curves represent longitudinal linear alterations in the form of ventricles, and may, under the condition of cardiac contraction, represent changes in volume of the cavities and consequently of volume output. The results are reported as changes in the degree of contraction.

In 30 dogs, they obtained increased contractions 24 times; while other phenomena of digitalization revealed by electrocardiograms were less constantly observed. In 14 cats the degree of contraction increased 4 times, decreased 6 times and was unchanged 4 times, with even more frequent effects on electrocardiograms than in dogs. The effect on contraction differed, therefore, in cats and dogs. Blood pressure readings were also made in some of the experiments in which ether was administered and the chest opened. In order to rule out the effect of these procedures, several experiments were performed on unetherized dogs without operative procedures; the blood pressure being obtained from the carotid artery which had been previously freed from the tissues of the neck (van Leersum's method). In these experiments the electrocardiographic and blood pressure changes were similar to those of the dogs on which operations were performed. From these experiments, the conclusions are drawn that digitalis and strophanthin with doses of therapeutic range increase the contractile power of the cardiac muscle, and by so doing, increase the volume output. This result supplies a firm basis for the statement that these drugs may exercise a beneficial action on the normally beating heart by their action directly on the cardiac muscle. Their results regarding blood pressure and electrocardiography will be mentioned when these phases of the digitalis problem are considered.

b. The effect on the electrocardiogram. The effect of digitalis on the T wave of the human electrocardiogram has furnished evidence of a different kind from that which has been discussed, and it has served as apparently clear proof that the drug acts directly on the heart muscle when administered in therapeutic doses. Although no direct relation has been established between the change in the T wave and the efficiency of the cardiac action, the discovery of this effect has been very useful in studying digitalis and has marked a definite advance in our knowledge.

Cohn and Fraser (22) first reported briefly in 1913 that they had "found that as the result of digitalis intoxication, the T wave in the electrocardiogram often becomes negative or diphasic, but returns to normal after the effect of the drug has passed off. It is an interesting fact that, although atropin may cause rate and conduction to return to normal, this change in the electrocardiogram persists."

The influence of digitalis on the T wave of the electrocardiogram was studied in a series of patients by Cohn, Fraser and Jamieson (23) who made the first comprehensive report on this subject, although a number of scattered observations on animals and man had been previously reported by others. Cohn and his coworkers found that an alteration of the T wave occurred in 30 of 34 patients to whom full doses of digitalis were given, and that this alteration was generally observed before alterations in rhythm or conduction time had occurred or before gastro-intestinal symptoms disturbed the patients. For the most part, the changes in the T wave consisted, first, in a diminution in the height of the wave, and finally in an inversion. In cases yielding downwardly directed T waves before treatment, digitalis produced eventually upwardly directed waves and other variations in the T waves occurred. This portion of the electrocardiogram was affected in patients with auricular fibrillation and flutter, and in one patient with complete auriculo-ventricular dissociation, as well as in those with normally beating hearts. It is pointed out that the sign attains greater importance on account of its appearance early after the beginning of the administration of the drug. Changes in the T wave were detected after an equivalent of 1.2 grams or even less of the dried leaves of digitalis had been given.

The influence of atropin on the altered T wave was repeatedly tested, and full doses of the drug intensified the changes in the T wave during its transient action. Atropin alone, however, produced no changes in the T wave. The altered T wave persisted for some days after digitalis was discontinued, resembling, in this respect, other effects of the drug.

In discussing their results, Cohn, Fraser and Jamieson bring forward convincing arguments to prove that the alteration of the T wave is caused by the action of digitalis on the heart muscle. The effect that atropin has on the phenomenon indicate, however, that

the cardiac inhibitors, the vagus nerves, are capable of exerting an influence upon it. The effect of full doses of digitalis on the T wave of the electrocardiogram of healthy children was studied by McCulloch and Rupe (112). They found that the drug did not produce the same effects as readily or as frequently as in adults as shown by the observations of Cohn, Fraser and Jamieson, although larger amounts of the drug per unit of body weight were given to the children, and other evidence of digitalis action was abundant.

Since the appearance of the paper by Cohn and his coworkers, their results have been abundantly confirmed, both for man and animals. Robinson and Wilson (134) found the inversion of the T wave was the first constant sign of digitalis action to be detected by electrocardiograms when the drug was injected intravenously into cats. It occurred in their series when approximately 25 per cent of the minimum lethal dose had been injected, and the dosage necessary for its production was not altered when the vagi were cut.

Cohn and Levy (25) have recently compared the effects on patients of g-strophanthin given intravenously with the effects of comparable doses of digitalis (digipuratum) given by mouth. Only a preliminary report has been published. They studied the relative effect of the two drugs on the T wave of the electrocardiogram and found that strophanthin had little or no influence on the form of the T wave, which at most underwent only transient changes, while the usual effects were produced by digitalis.

c. The effect on the size of the ventricles. Several attempts have been made to determine whether the administration of digitalis leads to the development of *hypertrophy of the ventricles*. Cloetta (18) found that the continuous subcutaneous administration of digitalis to young rabbits had absolutely no effect upon the size of their hearts, as compared with a series of controls. Of a series of animals in which aortic insufficiency was artificially produced, those treated with digitalis showed less cardiac enlargement than those that were not treated.

Caro (12), on the other hand, noted cardiac hypertrophy in animals to which digitalis had been given over a long period of time as did Reinike (125) who compared the cardiac muscle with the skeletal muscles. The latter muscles did not participate in the hypertrophy

observed in the heart. This work is based on a very small number of animals (four rabbits and two dogs) and so the conclusions drawn can hardly be considered as justified. Gelbart (58) repeated Cloetta's experiments with rabbits in which aortic insufficiency was artificially produced, and found that four weeks after the valve damage, cardiac hypertrophy had developed which was, in no way, influenced by digitalis. In view of the conflicting evidence, the relation of digitalis to cardiac hypertrophy must be considered as an open question.

The influence of digitalis on *cardiac dilatation* presents an important question. Although ventricular dilatation may be favorably effected by the administration of the drug it is impossible to say whether this result is brought about by direct action on the heart muscle or whether it is secondary to other beneficial effects.

d. Chemical aspects of digitalis action. The action of digitalis on the cardiac muscle has been studied from *the chemical view-point* by Burridge (8), who made some pioneer contributions which may bring results of fundamental importance to the therapeutic use of digitalis in the future. He has concerned himself especially with the interaction of digitalis and calcium on the perfused heart. He studied changes in the degree of cardiac contractions resulting from changes in the calcium content of the perfusion fluid. During some observations on the cardiac reserve, he found that calcium determines the amplitude or the percentage of the contractile material possessed by the heart which is used up with each spontaneous beat. And further that, under certain conditions, digitalis is a drug which enables a given tension of calcium in the perfusion fluid to evoke the activity of a greater proportion of the whole contractile material than is the case in its absence.

Burridge (9), in a second paper, discusses some factors of the cardiac mechanism illustrated by reference to certain actions of barium and digitalis. He interprets his experiments to mean that digitalis renders the heart more susceptible to calcium, as a given amount of calcium had more effect on the heart after treatment with digitalis than before. Crystalline digitoxin was used. He studied (*a*) the effect of digitalis on changes in the amplitude of contractions with fixed amounts of calcium, and with amounts of calcium necessary to evoke a fixed proportion of the whole contractile material;

(*b*) on the amount of tonus produced by a given amount of calcium and vice versa; and (*c*) on the amount of shortening of the refractory period produced by a given amount of calcium. Not only was calcium more effective but less calcium was required to produce constant effects after the heart had been exposed to digitalis. The response of the heart to calcium could be increased five to tenfold by treating it with digitalis, the effects of which persisted after the drug was withdrawn. The amount of calcium necessary to allow normal contractions may produce systolic standstill of a digitalized heart. A difference was noted in this respect, however, in hearts that had been long perfused and in fresh hearts, digitalis causing more marked effects in the latter.

Burridge believes that digitalis may be considered as a cardiac "lubricant," and should be classed with the secretions of the adrenals and pituitary gland in this regard.

Loewi (104) has also studied the relation of the effects of calcium and digitalis. He is of the opinion that in cases of heart disease the capacity of the heart for stimulation by the physiological calcium content of the blood is depressed. Strophanthin, Loewi believes, brings the sensitiveness of the heart to calcium back to normal.

These studies on the perfused heart represent conditions so far removed from those obtained in the treatment of heart disease that direct application is unwarranted. On the other hand, the work of Burridge and Loewi is very interesting and should not be lost sight of in attempts to find the fundamental principles underlying the action of digitalis on the human heart.

Levine (92) has discussed the question of whether the action of the digitalis bodies on the heart is a physical or a chemical process. His review of the work bearing on this question shows how difficult it is to find its answer. Certain facts indicate that probably chemical changes and physical action each play a part. The general condition of the heart, the temperature, rate and pressure of the perfusion system, and its organic and inorganic constituents are all factors difficult to resolve. Levine's perfusion experiments with strophanthin-g have led him to believe that the heart utilizes only a small portion (in the neighborhood of 10 per cent) of the drug to which it is exposed, regardless of the concentration at which it reaches the heart.

A toxic effect results when the heart has taken up a certain total of the drug, which is a definite small fraction of its own weight. If this theory be correct, it explains why, in concentrated solutions, the total amount is not important, for the small part that is taken out by the heart does not appreciably alter the concentration, while when very dilute solutions or small quantities are used, the amount taken up by the heart diminishes the remaining concentration appreciably; that is, the "digitalis pressure" becomes lessened. In these experiments, the rapid injections forced an adequate amount of strophanthin into the heart rapidly, and produced the toxic effect; in the slow injections, the same total amount of the drug was taken up by the heart, only more slowly.

2. The effect on the cardio-inhibitory mechanism.

Since the demonstration by the Weber brothers of the cardio-inhibitory mechanism, much interest has been shown in its relation to the action of drugs affecting the heart, and pharmacologists have had to take into account the possibility of indirect action of drugs on the heart through its nervous mechanism. The illuminating analysis of the cardiac action of the vagi by Engelmann has been of much value in attempts to understand the action of drugs affecting the heart. He showed that the heart possessed the properties of contractility, conductivity, rhythmicity and irritability, and that all these properties were depressed when the vagus nerves were stimulated. This conception has not only done much to form a basis for the explanation of abnormalities of the heart beat, but it has also been useful in understanding the effects that digitalis exerts on the heart.

a. Vagus stimulation. Traube was the first experimenter to find that cutting the vagus nerves altered the effect of digitalis on the heart. His later studies led him to conclude that digitalis stimulated the cardio-inhibitory centre in the medulla, and affected the heart through the vagi. Ackermann, according to Boehm (6) demonstrated in 1871 that digitalis failed to slow the heart of animals after atropin had been injected. Boehm, who was also one of the earliest experimenters with digitalis, concluded from his work with frogs, that the drug heightened the irritability of an inhibitory centre in the heart, and thus increased the susceptibility of the heart to vagus action.

Cushny (29) made an important contribution to the action of digitalis by his studies on the mammalian heart. He showed that the drug acted both by direct action on the muscle and by stimulation of the cardio-inhibitory centre. He divided its action into the inhibitory and the muscular stages, and concluded that the beneficial stage of its effect in heart disease resulted from its action on the heart muscle, while its inhibitory action was undesirable from the therapeutic standpoint. The fact that digitalis has two modes of action on the heart has made it difficult to reach definite conclusions as to their relative importance, and to give a clear conception of its effects.

Although the vagus effects of digitalis have been considered by most students of the subject to result entirely from the direct stimulation the cardio-inhibitory centre, other opinions have been held. Schmiedeberg (140) considers that vagus stimulation is secondary to the increased blood flow produced by the action of digitalis on the heart muscle. Kockmann (89) concluded from his experiments on dogs that digitalis causes slowing of the heart at least in part by stimulation of the peripheral end of the vagi. He obtained cardiac slowing in dogs by intravenous injections of various digitalis bodies after the vagi had been cut and found that this slowing was replaced by acceleration when atropin was given. Etienne (50) repeated these experiments and was unable to confirm Kockmann's observations.

Green and Peeler (60) studied the action of digitalis on the cardio-inhibitory centre when perfused through the isolated head and brain of the turtle. In their experiments, the head was completely isolated from the general circulation, and all tissues in the neck region except the vagus nerves were severed; the connection through the nerves being the only one maintained between the head and the body. The cardiac movements were recorded by a direct attachment of the ventricular apex to the recording lever. They found that when digitalis was perfused through the turtle's brain, the cardio-inhibitory centre was strongly stimulated and that not only was the rhythm of the heart inhibited, but the conduction of the cardiac impulses was also depressed. The weight of evidence is strongly in favor, therefore, of the conception that the vagus effects of digitalis on the heart are mainly or entirely the result of the direct stimulation of the cardio-inhibitory centre, although other factors may take some minor part in their production.

b. The effect on cardiac rate. The two chief cardiac effects of digitalis stimulation of the vagus centre are slowing of cardiac rate and depression of conduction of the cardiac impulse from auricles to ventricles. The other cardiac effects of vagus activity, inhibition of contractility and of irritability may be masked or overcome by the effect of the drug directly on the heart muscle, for they are not observed.

Reduction of the rate of the heart beat was the first digitalis effect to attract attention in experiments on animals, and these observations profoundly influenced the conceptions regarding the therapeutic use of the drug. Digitalis has been used by physicians for many years with the expectation of slowing the heart rate of patients in the same manner in which slowing is produced in animals. It is true that the reduction of the accelerated cardiac rate is without doubt the most important effect of digitalis in heart disease but this valuable effect occurs in a striking manner only in one form of cardiac disturbance, namely, auricular fibrillation, in which digitalis accomplishes the reduction of cardiac rate by an action quite different from that causing the slowing observed in animals and in man with normally beating hearts. This point will be discussed later when the use of the drug in auricular fibrillation is considered, but to avoid confusion, it is necessary to draw the distinction at this time between the action of digitalis on the normally beating heart and on the heart in which the auricles are in a state of fibrillation. It is only when these two conditions are differentiated that reliance can be placed on statements regarding the influence of the therapeutic action of digitalis on the cardiac rate. As it was not possible to determine with certainty the existence of auricular fibrillation before the employment of the electrocardiograph, only the literature of approximately the last ten years can be said to furnish reliable evidence on this point.

The question under discussion here is the ability of digitalis to slow the rate of impulse formation in the normally beating human heart by inhibition through the vagi of the rate of impulse formation.

Divergent opinions have been expressed by various students of digitalis. Wenckebach (155) states that the regularly beating heart is slowed by the action of digitalis on the vagus nerves and compared its action to the effect obtained by stimulation of the vagi by pressure

over their trunks in the neck. On the other hand, the drug was found to have almost no effect in most cases with normal rhythm in the series carefully studied by Mackenzie (107). He observed occasionally, however, striking slowing of the cardiac rate in cases with normal rhythm following the administration of digitalis, which he thinks is possibly due to the stimulation of the vagus nerves by the drug. Cushny (29) observed slowing of the heart in 6 of 18 patients with normally beating hearts to whom full doses of digitalis were given. The relation of the slowing in the cases in which it does occur due to vagus action was studied later by Cushny, Marris and Silverberg (32). They noted the effect of vagus paralysis by atropin in patients affected by digitalis, and attempted to distinguish between the effects of the drug directly on the heart muscle and those induced through vagus stimulation. They concluded that the effects produced through the vagi do not play any part in the beneficial action of the drug.

Cohn and Fraser (22) have reported repeated observations on the effect of digitalis on twelve patients with normally beating hearts. Daily electrocardiograms were taken and the drug was administered until a disturbance in the rhythm of the heart was effected, at which time the patients usually had gastric symptoms. In regard to the effect of digitalis on the heart rate they say:

> Slowing of the heart, even when the rhythm is normal, is still taken in many quarters as a measure of the efficiency of digitalis. The slowing of the heart which takes place *after* the onset of the symptoms of intoxication can hardly be taken to be of benefit. But before the symptoms occurred, slowing took place in only one patient, and this one was the subject of abrupt fluctuations in rate without the use of drugs. Slowing was observed in five more patients, but not until two days after rather severe symptoms of intoxication had set in. Two of these patients had quite normal hearts, anatomically and functionally. It appears then that if the patients are divided into two groups, those in whom slowing occurs before and those in whom it occurs after the onset of digitalis intoxication, slowing will rarely be observed in the first group—and the slowing which is observed in the second group is an effect which can, in the long run, scarcely be desirable.

In a later publication, Cohn (20) states:

We have been led to conclude from our observations that digitalis slows the sinus rhythm only in the group of hypodynamic hearts, and that to produce slowing is not a primary function of digitalis in therapeutic doses.

White and Sattler (160) report the effects of large doses of digitalis on ten healthy young adults. The effects of the drug were observed by daily electrocardiograms. Marked slowing occurred in two subjects, the heart rate reaching 43 beats per minute in each instance. In two other subjects, the heart rate became lower than usual at night when under the influence of the drug. In the other six cases, no change in heart rate occurred.

Parkinson (119) administered digitalis in full doses to 20 soldiers with cardiac symptoms, a rapid pulse rate and with normally beating hearts. (Effort syndrome.) He reports that the heart rate was reduced but little, and that the group of patients was scarcely influenced by digitalis. Pratt (122) states that his experience with digitalis confirms the findings of Mackenzie and Cohn and Fraser that digitalis rarely slows the rate of normally beating hearts until toxic symptoms are produced.

Robinson (130) has reported the effects of large single doses of digitalis on a series of approximately one hundred patients, and although striking effects were obtained in cases with auricular fibrillation, practically no change in the heart rate was observed in patients with normally beating hearts to whom the same amounts of digitalis were given.

On the other hand Sutherland (147) reports slowing of the normally beating heart by digitalis. He treated a series of cases of rheumatic heart disease with rapid cardiac rates, usually in children or in young patients. He states that digitalis caused slowing of the cardiac rate practically uniformly and the results in these cases were as definitely good as those usually seen in cases of auricular fibrillation.

McCulloch and Rupe (112a) have quite recently confirmed Sutherland's observations. They studied the effects of the drug on a series of children with heart disease, and found that slowing of the heart-rate of ten or more beats occurred so constantly when full therapeutic doses were given, that this effect could be used as a sign of digitalis action. They recommend the use of the drug in children with heart disease for the purpose of slowing the heart rate when it is more or less

persistently accelerated, and when such causes of acceleration as pain, fatigue, excitement and fever have been removed.

Pardee (118a) has also observed slowing of the normally beating heart following the administration of large single doses of the tincture. The onset of the slowing in the nine cases studied was noted to occur before the changes in the T wave of the electrocardiogram in three patients. The two effects occurred synchronously in four patients, while the T wave changes occurred first in two. The heart was considered as slowed when the rate was found to be ten beats per minute slower after the drug was given than in several counts before. The size of the single doses was determined by giving 1 minim of a fairly good tincture per pound of body weight.

Certain facts that have been demonstrated by animal experiments seem to show why the reduction of the cardiac rate is not more often seen in patients. Halsey (63) found that the dose which causes slowing and other signs of vague stimulation lay between 30 and 40 per cent of the minimum lethal dose of g-strophanthin, of digipuratum and of a fluid extract of digitalis given intravenously in dilute solutions in about fifteen minutes. Robinson and Wilson (134) slowly administered a diluted tincture of digitalis intravenously into a series of cats and followed the effects of the drug by electrocardiograms. In these experiments, the heart rate was slowed gradually, the effect being first seen with about 25 per cent of the minimum lethal dose, while the maximum slowing occurred when about 70 per cent of the minimum lethal dose had been given. In a second series of cats in which the vagi had been cut, practically no slowing of the heart rate was observed.

It seems evident that the amount of digitalis which is necessary to stimulate the cardio-inhibitory centre sufficiently to cause slowing of the heart-beat is usually greater than the amount that can be given to patients without the production of toxic symptoms. However, individuals whose vagus centres are more easily stimulated than usual or whose hearts are unusually susceptible to the slowing action of the vagi, are exceptions to this rule. Children apparently fall into this category. It is evident that the reduction of the rate of the normally beating heart should no longer be looked upon as an effect which digitalis should be expected to produce at least in adults although such an effect is desirable in many cases, of heart disease.

c. The effect on conduction. The depression of the conduction of the cardiac impulse between the auricles and ventricles has already been discussed briefly as a toxic manifestation of digitalis. As this effect plays an important part in the therapeutic action of the drug, and as it is at least in part brought about through the cardio-inhibitory mechanism, it deserves further consideration at this point.

The experimental studies of von Tabora (148) drew attention to the fact that digitalis depresses conduction through its action on the cardio-inhibitory centre. He concluded that this effect is produced both through the vagi and by the direct action of the drug on the conducting pathway. He also showed that digitalis is more effectual in animals when the A-V bundle had been injured.

Although the clinical recognition of the influence of digitalis on conduction has been general since it was first pointed out in patients by Mackenzie (106) there has been a discussion as to whether it should be regarded mainly as an effect of vagus stimulation or as an effect produced by the direct action of the drug on the heart.

Although the general opinion seems to favor the idea that vagus stimulation is largely responsible for the effects of digitalis on conduction, Cushny, Marris and Silverberg (32) concluded from their study of this problem on patients that the cardio-inhibitory mechanism is of minor importance, and they emphasize the direct action of digitalis on the heart. Cushny (31) expresses the opinion in a later publication, however, that digitalis may effect conduction by either method, and the condition of the heart is the factor determining which of the two methods will predominate. He seems to believe that in normal hearts the conduction is depressed through the inhibitory mechanism; while in diseased hearts, where conduction is already damaged, heart-block or delayed conduction is caused by the direct action of the drug.

Wedd (152) who studied the effect of atropin after full doses of digitalis in a large series of cases, concludes that in all cases the action of digitalis is both central, in the medulla, and local, in the myocardium. He observed that in 100 per cent of his cases of auricular fibrillation, and in 76 per cent of those with normal mechanism, the heart rate failed to return after atropin injections, to the level at which it was before being slowed by digitalis. He believes that it is

possible to measure the local action of the drug by the degree which atropin fails to restore the heart to its original rate. Wedd considers that Cushny has perhaps gone too far in ignoring the action of digitalis on the cardio-inhibitory centre in certain types of heart disease, in which the local action on conduction seems to predominate.

The observations of Cohn and Fraser (22) show clearly the manner by which digitalis affects the conduction of normally beating hearts when presumably not extensively damaged by disease. The twelve patients to whom digitalis was given until symptoms of intoxication appeared, were studied by means of electrocardiograms. In all but one, conduction was affected by the drug, as evidenced by lengthened conduction time or by blocked auricular impulses. The administration of atropin by subcutaneous injections caused the conduction to return practically to its normal condition, in all cases, regardless of the degree of depression that had been present. It is evident therefore that in these cases the effect on conduction was entirely produced by stimulation of the cardio-inhibitory mechanism, as it was abolished with vagus paralysis. The interesting observation was also made that the rate of the heart when reduced was not restored by atropin in a manner that paralleled the restoration of conduction.

White and Sattler (160) confirmed these observations in ten healthy young adults. They found that atropin completely removed the effect of digitalis on auriculo-ventricular conduction, and they concluded that the effect on conduction was almost entirely, if not entirely due to increase of vagal tone and irritability.

The foregoing observations demonstrate that the conducting system is capable of being effected by digitalis when the heart is presumably normal. However, depression of conduction does not become marked until large doses are given. Cohn (20) has observed delayed conduction forty-eight hours after the administration of the drug was begun, and in many instances, the conduction time gradually lengthened during the succeeding three to five days until partial block occurred. Heart block may occur, however, with extreme abruptness within a few hours. In the healthy young subjects studied by White and Sattler (160) the first effects on conduction were seen after 1.5 to 1.8 grams of the leaf had been administered; but there was no marked prolongation of the conduction time until 2.7 grams had been

taken. This latter dose is about that which, on an average, produces toxic symptoms.

There is no doubt that in heart disease when the tissues of the conducting pathway are damaged, digitalis heart-block may be produced by much smaller doses of the drug than those producing it in normal hearts, but it can no longer be said that digitalis produces heart-block only in hearts in which the conducting mechanism is already damaged. The problem of the conduction effects of digitalis in heart disease is a complicated one, and considerable light is still needed on this subject for its complete understanding.

Depression of conduction may be an important factor in the beneficial effects of digitalis in two ways. In the first place, it prevents the improper stimulation of the ventricles by the auricles. As will be seen when auricular fibrillation is discussed, the ability of digitalis to prevent stimuli from reaching the ventricles is of paramount importance in the treatment of certain forms of heart disease. In the second place, depression of conduction allows a longer period to elapse between auricular and ventricular systole, and Cohn and Fraser (22) have suggested that this may be a matter of some importance in the treatment of patients who have mitral stenosis. They point out that in these patients,

> the initial and most important of the factors which tend to disturb the circulation is the narrow auriculo-ventricular orifice, which prevents the complete empyting of the left auricle within the time allowed before the ventricles contract. If one could lengthen the conduction time and could keep it lengthened, thus separating the contractions of the auricles and ventricles as widely as possible, much aid could be given patients of this class in maintaining a satisfactory circulation. There is reason to believe that this can be done.

3. The effects on the blood vessels

a. The effect on blood pressure. Cushny (28) states that Blake discovered in 1839 that digitalis caused an elevation of blood pressure in experimental animals. From that time until quite recently, this effect and the effect on the heart rate have almost predominated the field of digitalis action. It was generally believed that the arterial pressure was raised by increased force of the ventricular contractions

and by the constriction of the blood vessels. It is an interesting fact that neither of these effects has been demonstrated in man as a direct action of the drug, although there is indirect evidence that the first of these effects occurs, as was pointed out, when the action of digitalis on the heart muscle was considered. The effect of digitalis on the blood pressure is of such importance that it is desirable to consider briefly some of the experimental work bearing on this subject before reviewing the more recent clinical studies.

The chief exponents of the idea that digitalis has a direct action on the blood vessels have been Gottlieb and the members of his school. Numerous investigations have been reported from his laboratory bearing on this subject.

The most important study to lead to the belief that the digitalis bodies are capable of producing marked vascular constriction through direct action on the vessel walls has been, according to Eggleston (43) that of Gottlieb and Magnus, published in 1902. By the use of doses of various digitalis bodies which were five to fifteen times the minimum lethal dose, they produced striking elevation of blood pressure in experimental animals, which was in part caused by constriction of the splanchnic vessels by direct action of the drug upon their walls.

Among other publications from Gottlieb's laboratory which are of interest, several may be mentioned. Kasztan (87) in 1910 showed that when Ringer's solution containing not more than 0.05 mgm. of crystalline strophanthin to 100 cc. was perfused through the kidneys of dogs, cats and rabbits, arterial dilatation took place; while if the solution contained 0.1 mgm. of strophanthin, arterial constriction occurred. The weaker solution when perfused through the intestinal vessels, however, caused them to constrict. This work was confirmatory of that of Jonescu and Loewi (85), who considered that dilatation of the renal vessels occurred as a direct peripheral effect on the vessels. Fahrenkamp (51) repeated the work of Kasztan, using, however, digitoxin instead of strophanthin. He obtained an effect on the renal and intestinal vessels, similar to that observed by Kasztan. He found further that concentrations of digitoxin which contracted the kidney and intestinal arteries had no effect on the vessels of the skin and muscles. Cats and rabbits were used, and Fahrenkamp found that 0.7 mgm. of digitoxin per 100 cc. Ringer's solution caused dilatation

of the renal vessels of the cat; that 0.48 mgm. produced the same effects in rabbits, and that 1.2 mgm. of digitoxin caused contraction of these vessels in both animals.

Later Joseph (86) investigated a similar subject in Gottlieb's laboratory and studied simultaneously the effect of small doses of strophanthin and digitalis (digipuratum) on the heart and on the vessels. He attempted to use doses comparable to those employed in the therapeutic use of these drugs; but, as a matter of fact, his doses appear to be considerably larger as a rule. He found that in rabbits and cats the action of these drugs on the heart and on the vessels are not synchronous and that they seem therefore to be independent. Digitalis was found to cause at first a dilatation and then a constriction of the vessels, which in the intestines, outlasted all other effects. The kidney vessels dilate while the intestinal vessels contract. Joseph considers that he succeeded in demonstrating vascular effects with any dose that affected the heart. The slowly developing and persistent narrowing of the intestinal vessels is the most frequent and most striking digitalis effect which he observed.

Gottlieb (59) has laid great stress on these and similar investigations. He holds the view that the power of digitalis to alter the size of important vascular systems is of prime importance, and that the alteration of the distribution of the blood which digitalis causes is the main factor in its curative action. He believes also that the vascular changes caused by digitalis are, in large measure, responsible for an elevation of the blood pressure in man when the drug is given in therapeutic doses.

Krehl (90) has also recently stated that he considered the best results from the use of digitalis were obtained in patients in which there is altered blood distribution.

Eggleston (43) has recently published a critical review of the investigations of the Gottlieb school and has commented upon their bearing on the question of *blood pressure* changes caused by digitalis in man. He points out especially the great divergence in dosage under the two conditions and says

> it must be quite obvious to anyone who gives the matter a moment's thought that it is utterly fallacious to reason from such experiments that similar effects would be produced in man from the therapeutic use of digitalis or its congeners.

The discovery that elevation of blood pressure is not a constant or conspicuous effect of digitalis in man occurred when the sphygmomanometer was introduced into clinical medicine, and when accurate objective observation began to replace deductions from animals and observations strongly influenced by preconceived ideas. In 1901 Sahli (quoted by Eggleston) stated that in cases with circulatory stasis and high blood pressure, digitalis not only relieved the stasis, but also very often reduced the blood pressure by from 30 to 40 mm. of mercury. The findings of Sahli have been amply confirmed by such careful students of the effects of digitalis on man as Mackenzie (108), Cushny (29) and Cohn (21). Eggleston (43) has summarized the findings of a number of observers[1] who have studied the effect of digitalis on blood pressure. He says:

We find that the systolic blood pressure was recorded for 181 cases. In 66 of these, or about 36 per cent, the systolic pressure is stated to have risen or to have tended to rise; in 57 or 31 per cent, it fell; and in 58, or 32 per cent, it is recorded as having shown no change. In 116 instances in which the diastolic pressure is mentioned, it is stated to have been increased in 24, or 15 per cent; and to have fallen in 76 or 65 per cent. While the actual extent of the changes is not always stated, it would seem that digitalis is about as likely to influence the systolic pressure in one direction as in another, or not to alter it at all. With the diastolic pressure, however, the chances are nearly two to one that digitalis will cause some reduction, and the chances are more than three to one in favor of its reducing it as compared with the likelihood of its raising it. Other things being equal, this evidence certainly does not point to the occurrence of any marked vasoconstrictor action of the drug in man. The opinions expressed by the several authorities cited are in very general agreement that digitalis has little constant influence on the systolic blood-pressure when used therapeutically, and some even go so far as to suggest that it actually often causes some vasodilatation which would account for the reductions observed in the diastolic pressure.

Eggleston's own observations have been perhaps the most valuable contribution to the study of the influence of digitalis on blood pressure

[1] The work here summarized is that of Czyhlarz, Gross, Neu, Geisböck, Schwartz, Fellner, Szinnyei, Price, Lawrence and Cadbury. References to their papers are given by Eggleston.

in man. The various conditions of the study were carefully controlled. An assayed extract of digitalis or digitoxin in the form of tablet triturates or of the granules of Nativelle's digitaline crystalisée were given in large doses. The full amount calculated, according to body weight, was administered in twelve or eighteen hours and the effects of the drug on the heart were followed by polygraphic and electrocardiographic methods. The blood pressure was recorded for three days before and three days after the drug was given. Eggleston's series consist of 14 patients, 6 of whom had high initial pressure while 8 had normal or low initial pressure. His study revealed the fact that

> the administration of large doses of digitalis or digitoxin has very little tendency to elevate the systolic pressure, this having been increased by 11 mm. of mercury in one, and 15 mm. in a second case. In only one case was the systolic pressure materially reduced, namely by 23 mm. of mercury. On the other hand, the diastolic pressure was significantly lowered in 7, or 50 per cent of the cases, while it was never significantly raised.
>
> It is evident, therefore, that digitalis and digitoxin have very little influence on the systolic pressure in either direction, that they tend to produce a significant reduction in the diastolic and more decidedly, to produce a material increase in the pulse pressure.

Eggleston found that alteration in the pulse rate did not offer an explanation for the changes occurring in the diastolic pressure. The facts brought out by this study abundantly warrant the conclusion that "there is no evidence that either digitalis or digitoxin has any direct action on the vessels when given to man even in large therapeutic doses."

Eggleston's observations show that the net changes in the systolic, diastolic and pulse pressure differ in different cases in order best to meet the condition prevailing, and they indicate that studies on the blood pressure effects of digitalis must always take into strict account the condition of the patients under observation.

It will no doubt be some time before clinicians generally learn that arterial hypertension does not contraindicate the use of digitalis, but may in fact be advantageously affected by its action. However, clinicians have reported favorable results from the drug in cases with elevated blood pressure. Windle (162) has recently stated that

digitalis is valuable to patients with degenerated arteries, high blood pressure and anginal symptoms and may bring about an immunity from angina. Lawrence (91) has expressed similar views after a careful study of the blood pressure in 26 cases, during treatment with digitalis. Danielopolu (34) treated 36 cases of arterial hypertension with Nativelle's digitaline, although he remarks that the work dealing with the action of digitalis on the arteries made him hesitate to do so. His patients had arterial sclerosis and nephritis. Of the 36 patients a fall in the systolic pressure occurred in 19, while in 24 patients, the diastolic pressure was reduced: In 2 patients, a fall in systolic pressure alone was observed. The reduction of the arterial pressure amounted to 10, 20 or even 30 mm. of mercury.

During a study of one hundred patients, some of whom had hypertension, to whom very large single doses of the tincture of digitalis were given, Robinson (130) noted that the systolic pressure tended to approach more nearly the normal level after the drug was given. In other words, elevated blood pressure fell, while abnormally low pressure rose after the drug was given. These observations confirm Eggleston's more detailed study.

It is by no means desirable that the state of the blood pressure should be no longer taken into consideration in determining the indications for the use of digitalis or in studying its effects in man. Recent experimental observations by Cohn and Levy (26) indicate that under conditions kept as nearly similar as possible to those pertaining in the clinical use of digitalis, the blood pressure of dogs may be elevated by g-strophanthin and the tincture of digitalis. During a study of the effects of therapeutic doses of digitalis on the contraction of the heart muscle, they studied the blood pressure of normal dogs when not under operative conditions by the method of van Leersum, and noted the effect of the drugs used when given in doses on the same body weight basis as used in patients, which produced no evidence of severe intoxication. In the few animals thus studied, they found that the blood pressure usually rose, the increase varying from 20 to 66 mm. of mercury.

Cohn and Levy seem to attribute the rise of blood pressure which was transient, to the effect of the drugs on the contraction of the heart muscle.

It is not possible to dismiss the subject of the effect of digitalis on blood pressure as non-existing, but the older ideas must give place to those resting upon the accurate clinical studies that have been made since the introduction of the sphygmomanometer, and arterial hypertension must not be accepted as a reason *per se* for withholding digitalis when it is otherwise indicated.

b. The effect on the coronary circulation is a subject about which there has been a certain amount of speculation and which has also been studied experimentally. Although theoretically it is of much interest, practically, no facts have been established which bear directly on changes in the coronary arteries with therapeutic doses of the drug, and no definite information regarding the effect of digitalis on the coronary circulation of man has been obtained.

Eggleston (47) has recently reviewed this subject. He points out that it assumes some importance because of statements that appear in some recent textbooks to the effect that digitalis may cause a dangerous constriction of the coronaries, and is therefore contraindicated in angina pectoris. There seems to be no evidence for the idea that digitalis causes coronary constriction. The experiments of Felix Meyer and of Sakai and Saneyoshi (quoted by Eggleston) have shown that the coronaries do not contract under the influence of digitalis but if they are affected at all, they probably dilate. Bond (10) investigated the influence of digitalis and strophanthus on the coronary blood flow of dogs, measuring the coronary flow by the number of drops in a given interval of time coming from the coronary veins. He could find no effect attributable to these drugs, and concluded that the coronary blood flow is probably regulated by the systemic blood pressure, as it was decreased when the blood pressure was lowered by nitroglycerin and amyl nitrate.

Voegtlin and Macht (150a) investigated the action of a number of drugs of the digitalis group on strips of mammalian coronary arteries. They found that digitoxin, crystallized German digitalin of Merk and bufagin especially caused coronary constriction under the conditions of their experiments, while digitonin and preparations containing this saponin-like body caused relaxation. Strophanthin was found to be practically inert in this respect. Voegtlin and Macht think that these observations have considerable importance in the therapeutic use of

digitalis especially in the treatment of angina pectoris, when they believe a nitrite which they find causes coronary relaxation should be combined with the digitalis.

Eggleston (47) also discusses the relation of the blood supply to the heart muscle through the coronaries to pulsus alternans, and expresses the opinion that although this derangement of the heart may occur apparently as a result of digitalis, this is no reason for considering that digitalis brings on this derangement by coronary constriction. Pulsus alternans may also disappear when digitalis is given.

It is safe, therefore, to say that at present there is no reason to believe that the digitalis bodies affect the blood flow through the coronary arteries by direct action on these vessels.

c. The effect on the venous blood pressure in man has been studied by Capps and Matthews (11), who used both digitalis and strophanthin, and obtained no evidence of changes in the venous pressure.

4. The effects on the kidneys

The use of digitalis as a diuretic begins with its introduction into medical practice in 1785, as Withering (163) recommended it especially for the removal of dropsy and emphasized its action on the kidneys rather than its action on the heart. Withering mentions diuresis as one of the cardinal effects of digitalis, and recommends that its occurrence should be taken as an indication for discontinuing its administration.

The manner in which digitalis causes diuresis has been one of the controversial points regarding the action of the drug. The chief discussion has arisen over the question as to whether diuresis is in reality a direct effect of the drug on the kidney and its vessels, or whether it is secondary to an improved state of the general circulation. Various opinions are held regarding this point.

The experimental studies of Gottlieb and Magnus, Jonescu and Loewi (85), Kasztan (87), Fahrenkamp (51), and Joseph (86) have already been referred to in discussing the action of digitalis on the blood vessels. The fact that dilatation of the renal vessels is caused by weak solutions of the digitalis bodies cannot, as it was previously pointed out, be taken as evidence from which conclusions can be drawn regarding the effects of therapeutic doses of the drug in man.

The conditions are far from comparable. On the other hand, these experiments clearly indicate that the kidney vessels differ in their reaction to digitalis from other vessels, especially those of the splanchnic area. This fact is inviting as a basis upon which to build a theory of digitalis diuresis, as Gottlieb and others have done. Generally speaking, the ground is considered insecure, and the results of clinical studies show that the diuretic effects of digitalis do not occur as they would were the theory of Gottlieb correct. The quantitative study of diuresis has recently been much improved by the organization in hospitals of means of accurately measuring the intake and output of fluids of patients and accurate records of body weight.

Since the introduction of such methods, Mackenzie (108) has reported that diuresis is not very evident in patients even when digitalis is given to the stage of toxic symptoms, and he considers that no definite conclusions are justified regarding diuresis from his careful study of the action of digitalis. Cushny (29) observed diuresis only in patients in whom dropsy was present, and Agassiz (2) obtained similar results from the intravenous administration of rather small doses of strophanthin in cases of auricular fibrillation. Diuresis occurred only in the presence of edema. Cohn (20) has also emphasized this distinction, and reports that in the group of patients which he studied with much care, diuresis was never seen in patients without edema. He concludes from his experience that a specific effect on the urinary output does not occur as the result of giving digitalis to patients with normally beating hearts without the presence of edema. Cohn (21) has also found that diuresis is usually marked when edema is present. Christian (16) in emphasizing the beneficial effects which may be obtained from digitalis in chronic cardiac cases with edema in whom there was no irregularity of the pulse, points out the striking diuresis and loss of body weight which may occur in these patients, and publishes a series of charts illustrating his results. There seems to be in his cases a relation between the amount of edema and the extent of diuresis. The reports of other observers tend to confirm these findings. It is evident that some factors other than dilatation of the renal vessels take part in the increased flow of urine produced by digitalis. The question of the effect of digitalis on water exchange has been recently discussed

by Krehl (90) who is no doubt more or less influenced by the views of his colleague, Gottlieb.

The question of the action of digitalis on the kidneys has been investigated by Reinike (124) by an experimental method differing from those already mentioned. Digitalis was administered over a long period of time to rabbits, and was found to cause an enlargement of the kidneys as compared with those of control animals. This suggested that the kidneys had undergone excessive activity under the influence of the drug. No definite conclusions, however, are justified from Reinike's experiment, as the drug was given to only four animals, and they did not show uniform results.

In spite of the fact that there is nothing definite on which to base a claim that digitalis produces diuresis by direct action on the kidneys, the position that the kidneys play no part in digitalis diuresis, does not seem to be entirely justified. However, several pharmacologists who have been especially interested in the action of the drug state that diuresis is entirely a secondary effect.

Hatcher (70) says:

> None of the drugs of this group are actively diuretic through any direct action on the kidneys. They induce diuresis solely through an improved circulation. That does not mean either a higher or a lower blood presure in every case; it means a more effective circulation, one better adapted to the needs of the individual patient. This sometimes means an increase, sometimes a decrease, in pressure.

Sollmann (143) holds a similar opinion regarding the diuretic action of the drug.

In Eggleston's (47) most recent paper on digitalis, he says:

> While it has been claimed that digitalis exerts a specific diuretic action on the kidneys, or that it produces diuresis by selective vasodilatation of the renal arterioles, the evidence for these claims is quite unsatisfactory, and careful studies have shown conclusively that the drug is not a diuretic in normal animals. It has also been observed repeatedly that no diuresis follows the administration of digitalis to normal human beings or to those with heart failure uncomplicated with edema or serous effusions. In cases of nephritis with edema, or even with general anasarca, digitalis also produces no diuresis when heart failure is not associated with the nephritis.

When, however, heart failure is accompanied with edema or anasarca, profuse diuresis may follow the administration of digitalis, but this is found to occur only when the heart failure is more or less effectively overcome by the drug, and when the heart failure is not affected, no diuresis ensues from its administration. It is clear, then, that the diuretic action of digitalis in man, is essentially secondary to its capacity to relieve heart failure and restore the circulation; and when it is effective in edematous cases of heart failure, it is often one of the earliest of the manifestations of the action of the drug, though other evidences can be detected if looked for. When adequate digitalization fails to produce diuresis in a patient with edema and heart failure, it will almost invariably be found that either the heart failure has not been relieved or that the failure is complicated by nephritis, which then demands appropriate treatment.

At variance with Eggleston's idea regarding the relation of nephritis to digitalis diuresis are the findings of Hedinger (quoted by Edens, 37) that digitalis has a direct diuretic action on the diseased kidney, which is independent of its action on the heart. However, there is considerable chance for differences of opinion as to what is meant by a diseased kidney.

The idea that pathological changes may influence the effect of digitalis on the kidneys appears again in a recent paper by Jarisch (84). He reports two cases of syphilitic aortitis in which diuresis was inhibited by therapeutic doses of digitalis but was increased by very small doses. Jarisch makes use of an idea of Meyer (113) in order to explain these results that increased excitability of the renal vessels lowers the threshold for both the vasoconstricting and vasodilating action of digitalis. He suggests that both patients had increased excitability of their renal vessels as the result of the incipient stage of contracted kidneys that was present. He states that his findings are in accord with those of Meyer who found that in early nephritis diuresis was produced by smaller doses than when the kidneys were normal. Jarisch considers that small doses of digitalis should be used when nephritis is present, and that caution as to dosage should be used in heart cases that have low specific gravity of the urine, which points to renal sclerosis.

The relation of the output of urine and alterations in blood pressure has been studied by Lawrence (91) who found that in his 26 patients,

diuresis was always accompanied by a fall in blood pressure, and 88 per cent of the cases showing a fall of blood pressure had diuresis. These findings, although of interest, do not, at present, add evidence of value in determining the manner of production of diuresis by digitalis.

The question as to a primary or direct action of digitalis on the kidneys or its vessels in cases of cardiac failure with edema, should be considered as yet unsettled, although it has been abundantly demonstrated that digitalis has no diuretic action except under very special conditions.

Cohn (20) has reported that a diminution in the output of urine is sometimes seen when well marked toxic symptoms appear. This phenomenon is adequately accounted for, he believes, by the presence of nausea and vomiting, which diminishes the fluid intake and may result in the loss of considerable fluid by emesis. This observation is confirmatory of a statement by Withering who said that large doses of digitalis may check the flow when smaller doses had increased it.

IX. THE USE OF DIGITALIS IN HEART FAILURE

Digitalis has attained the reputation of being the most valuable drug in the treatment of heart disease, and by the term heart disease is usually meant a group of symptoms such as dyspnea, cough, chest pain, edema, cyanosis, weakness, and palpitation. These symptoms are in reality not evidence of heart disease, but of heart failure, and they occur as a group only when the heart is unable to maintain the normal circulation of the blood. Heart failure may result from a variety of cardiac disorders; some of which are much more susceptible to a favorable influence by digitalis than others. The great reputation of the drug in heart disease doubtless rests upon the striking benefits which it produces in cases of heart failure dependent upon one particular type of cardiac derangement. On the other hand, fault has been found with the drug when it has been used in heart failure dependent upon other causes with the expectation that similar results are to be obtained. In considering the therapeutic use of digitalis, it is just as necessary to take into account the various cardiac derangements responsible for heart failure as it is the effects produced by the drug.

In fact, it is only when these two aspects of the subject are brought together that a rational basis for the therapeutic use of the digitalis bodies can be established. It is undoubtedly because clinicians have not fully understood the action of digitalis and because pharmacologists have not fully understood heart failure, that so many misconceptions have existed in the past regarding the therapeutic use of digitalis. The coöperation of clinicians and pharmacologists which has recently come about has been responsible for some of the most valuable contributions to the present-day knowledge of digitalis. Examples of this coöperation and collaboration are those of Mackenzie and Cushny in England and of Eggleston and Hatcher in America. This type of coöperative work is greatly to be desired, and is destined to bring forth results of great value in many fields of medicine.

1. Classification of heart failure

In the following part of this review, the relative value of digitalis will be discussed in the various disorders of the heart which are commonly seen; and which may lead to the failure of that essential organ to maintain an efficient circulation of the blood. Cohn (20) has emphasized the desirability of considering the action of digitalis in its relation to various forms of heart failure, which he has divided for this purpose according to the following table.

A. Normal rhythm	a. Without edema	1.	With normal blood pressure
		2.	With high blood pressure
	b. With edema	3.	With normal blood pressure
		4.	With high blood pressure
B. Auricular fibrillation	a. Without edema	5.	With normal blood pressure
		6.	With high blood pressure
	b. With edema	7.	With normal blood pressure
		8.	With high blood pressure

This classification shows the importance Cohn has placed upon the type of cardiac rhythm, the presence of edema and the state of the blood pressure in the reaction of the heart and circulation to digitalis. He has discussed his observations on the action of the drug in patients with normal cardiac rhythm, without edema and with normal blood

pressure; and a comparison of the action of the drug in these patients with those in other groups has led him to conclude as follows:

> It seems important to emphasize the fact that it is essential to distinguish differences which patients suffering from heart disease present and to study them in groups, with these differences in mind. Rhythm certainly offers a prime basis. The effect of digitalis on rate and on a number of other capacities varies with the nature of the disturbed function.

In actual practice, it is often impossible to classify sharply cases of heart failure on the basis of the derangements of function underlying their production. Nearly every case results from a combination of causes, and these causes must be evaluated relatively to one another, in any attempt to arrive at a clear understanding by which treatment may be intelligently instituted. The ability to determine the relative importance of the various factors underlying the production of heart failure is an essential requirement for its successful treatment. The disorder of the heart revealed most prominently by all the means of examination now available may often be unimportant or only contributory in the production of heart failure in any particular case. The relative importance of valvular and muscular lesions of the heart may be cited as an example. In many cases, a valvular defect obtrudes itself upon the physician, while muscular inefficiency, so difficult or impossible to determine directly, is in reality the actual cause of heart failure. It is necessary to point out the difficulties regarding the classification of heart failure on the basis of its causation, because a discussion of the effects of digitalis in this relation to the various disorders of the heart cannot take into account many of the practical problems involved in the use of the drug in the treatment of heart failure. These can only be solved by the careful study of patients, in whom a great variety of conditions and circumstances are encountered, calling forth constantly the exercise of clinical judgment, which cannot be acquired from books, but only at the bedside or in the consulting room.

2. Disturbed cardiac mechanism

a. Auricular fibrillation. Following the suggestion of Cohn, rhythm is taken as a prime basis for distinguishing the various types of

disorders of the heart, and those disorders associated with or consisting of disturbed cardiac mechanism will be considered before those with normal mechanism and regular beating hearts are taken up. It seems desirable to adopt this order and to discuss first the use of digitalis in auricular fibrillation, because it is in this type of deranged cardiac rhythm that digitalis produces its most brilliant results, a point which it is well to emphasize at the outset.

A clear understanding of auricular fibrillation is essential for the intelligent employment of digitalis. It has been especially well described by Lewis (100, 101), to whose work the reader is referred.

The salient features by which this condition is recognized may be summarized as follows: The pulse and the cardiac sounds occur irregularly without any order to the arrhythmia, and usually with a considerable increase in rate. There is no evidence of the normal auricular contractions in the veins of the neck, as shown by polygrams, and the auricular waves, the so called P waves, of the electrocardiogram disappear. A constant succession of small waves may sometimes be seen in the venous pulse curve, while the electrocardiogram shows almost constantly a series of small rapidly recurring waves, lacking uniformity and well defined form, seen throughout the diastolic portion of the curve. All these phenomena are readily appreciated when it is realized that the auricles no longer contract as a whole in a rhythmical fashion, but stand in diastole with their separate fibers contracting and relaxing one after another constantly. This abnormal type of auricular action sends down impulses to the ventricles more frequently than the normally beating auricles and the rhythmical character of the impulse formation is lost. A rapid irregular ventricular action therefore results which is distinctly less efficient in the maintenance of the circulation than is the slower regular normal beat. This increase in rate is often an important factor in the failure of the heart when auricular fibrillation is present.

Auricular fibrillation was recognized as a common disturbance of the human heart-beat in 1909, when Rothberger and Winterberg and Lewis simultaneously demonstrated its existence by means of electrocardiograms. Several years previously, however, Mackenzie (108) drew attention to the fact that there were striking differences in the effects of digitalis in cases with irregular heart action and in cases

with regular rhythm, and he stated that "no rational idea of the manner in which digitalis acts can be obtained unless this change in the heart's action is appreciated." He was also perhaps the first to study the effect of digitalis in patients with auricular fibrillation after this condition became established as a clinical entity. His paper which appeared in 1911 was followed shortly by important contributions by Cushny (29) and Edens (37) and, since that time, the value of digitalis in this condition has been generally recognized. It is scarcely necessary to review the papers of other students of this subject, such as Fahrenkamp (52), Fulton (56), Christian (14), Robinson (128), Weil (153), Cohn (20), Borultau and Stadelmann (7), Pratt (122), Wedd (152) and others who have all borne witness to the striking benefits obtained by the use of digitalis in auricular fibrillation. Their papers are referred to in regard to special phases of this subject.

It has been repeatedly shown that the great value of digitalis in auricular fibrillation lies in the fact that the drug slows the abnormally rapid and irregularly beating ventricles, and this effect of the drug is generally considered its most important accomplishment. Lewis (99) has recently expressed what is perhaps an extreme view of this matter. He says:

> The chief value of digitalis lies in the power to control the ventricular rate when fibrillation of the auricles has come. In most patients in whom this disorder of the heart is discerned, the ventricles beat rapidly, at rates of 120, 140, 160 and even more per minute. It is this rapid action which fatigues the heart, and digitalis, by lessening the rate, lessens the fatigue. The normal heart rate, while the body is at rest—to take approximate and convenient numbers—is 60 beats to the minute. Each ventricular cycle lasts one second; of this, one-third is occupied by systole; two-thirds by the resting period of diastole. The heart works one shift and sleeps for two. But if the rate is 120 beats to the minute, then each cycle lasts half a second; systole lasts quarter of a second and so does diastole. Work and rest alternate in equal shifts. As the rate of beating rises, so is systole increased relatively at the expense of diastole. Very important is it, therefore, to reduce the heart rate when this is excessive. A chief cause of rapid heart action when heart failure threatens or has come, is fibrillation of the auricles, and it is in this condition that digitalis acts so beneficially; it reduces and holds the rate within normal bounds.

The reduction of accelerated ventricular rate is the only important action of the drug upon the human heart of which we have knowledge. There are few, if any, instances, of which we know with certainty, in which digitalis acts beneficially, except cases of accelerated action; there are few instances of acceleration in which the drug produces unquestionable benefit apart from those provoked by fibrillation of the auricles.

The principle of digitalis therapy—and when I speak of digitalis, I include the allied drugs, strophanthus and squills—is that, administered to suitable cases, the heart, by means of it, obtains rest. The giving of this drug to unselected cardiac cases is much to be deplored. Those who regard digitalis as a cardiac stimulant mistake its character; its chief action is to rest the heart. To the heart, foxglove is not tonic, but powerfully hypnotic. It controls the diastoles of the heart; it extends the period of sleep.

Although most students of digitalis do not share entirely the idea of Lewis regarding the relative uselessness of the drug in conditions other than auricular fibrillation, he has well expressed the consensus of opinion regarding its use in auricular fibrillation.

Agassiz (2) has treated a series of cases of auricular fibrillation with small doses of strophanthin administered intravenously and has shown that this drug has a very similar action to that of other members of the digitalis group when employed upon cases of auricular fibrillation. He states that it is a powerful and serviceable remedy when a rapid reduction of the heart rate is desired in cases of auricular fibrillation in young subjects or in those cases which give a history of rheumatism. The heart rate may be reduced from 180 or 160 to 100 or 80 per minute within six or eight hours. Agassiz's method of administration of strophanthin will be taken up later.

As stated previously, the slowing of the heart is brought about by a different mechanism than that by which digitalis slows the normally beating heart. When the auricles are fibrillating, stimuli are sent down to the ventricles unrhythmically and at a rate much higher than from the normally beating auricles. Digitalis depresses the conductivity of the pathway between the auricles and the ventricles, which then allows fewer stimuli to pass. In this way, the rate of the ventricles is slowed and the arrhythmia reduced. This effect is very desirable because the rapid irregular ventricular activity which

the fibrillating auricles engender is much less competent to maintain the circulation than the ventricular activity of normally beating heart. The ventricles become more competent when they are slowed and regulated by digitalis. The tumultuous action of the fibrillating auricles is not appreciably affected by digitalis as revealed by electrocardiograms. The manner in which digitalis affects the conduction of the cardiac impulse has been already considered.

The question has been raised whether other factors may not enter into the slowing of the ventricles which digitalis produces in hearts with auricular fibrillation, which are not involved in the depression of conduction in the normally beating heart. Cushny has been especially interested in this subject, and has raised the question as to whether the action of digitalis on the cardio-inhibitory centre is the important factor in slowing the ventricles in auricular fibrillation. Cushny, Marris and Silverberg (32) found that the ventricular rate, slowed by digitalis, was not restored to its original rate when the vagi were paralyzed by atropin. They came to the conclusion that in auricular fibrillation, the ventricular slowing was accomplished by other means than by stimulation of the cardio-inhibitory mechanism, which seemed to play no part in the action of digitalis in auricular fibrillation.

They believe that the conductive pathway from auricles to ventricles becomes less excitable when the nutritional condition of the tissues is improved, and that this improvement may result not only from the increased efficiency of the circulation brought about by the direct action of digitalis on the ventricular muscle, but also by lessening the demands on the heart by rest. They explain in this way the ventricular slowing which occurs when patients with auricular fibrillation are put to bed. Their hypothesis calls for the existence of abnormally increased conductivity in the hearts of patients with auricular fibrillation caused by malnutrition of the tissues. This idea is hard to accept in the light of the state of conduction in other types of heart disease in which it can be accurately determined, and is not infrequently found to be decreased.

In a later publication, Cushny (31) gives the results of further work on this subject in which he attempted to reproduce the cardiac condition of cases of auricular fibrillation in perfused hearts. He states

his belief in two independent reactions of conduction to therapeutic doses of digitalis. The first is that observed in the normal heart of experimental animals and in the normally beating human heart. It is the result of stimulation of the cardio-inhibitory centre.

The second is that observed in cases of auricular fibrillation in man, and results from the direct action of the drug on the conducting system. Cushny believes that the ventricular slowing which digitalis produces in cases of auricular fibrillation is independent of the action of the drug on the inhibitory mechanism, for it is not prevented by atropin. The primary reason why digitalis acts directly on the conducting mechanism in these cases is the malnutrition of the heart and auricular fibrillation merely favors its appearance by accentuating the fundamental cardiac malnutrition. Wedd (152) has also studied a number of cases of auricular fibrillation and has injected atropin during thorough digitalization. He has come to the conclusion that in all cases digitalis affects conduction both by its stimulation of the cardio-inhibitory centre and by its direct action on the heart, with relatively greater local action in auricular fibrillation. Exception is taken to the statement of Cushny that in fibrillation there is no digitalis action through the inhibitory mechanism. Eggleston (47) has recently discussed Cushny's experiments and conclusions and is in substantial agreement with Wedd.

It is well known that some cases of auricular fibrillation are unusually susceptible to digitalis. Robinson and Draper (132) have shown that in cases of auricular fibrillation prolonged stoppage of the ventricles may be brought about by pressure over one of the vagi of the neck. Weil (154) has also found vagus pressure more effectual in auricular fibrillation than in other conditions, a result which he attributes to an impaired state of the heart. He also found that the normally beating hearts of patients to whom digitalis had been given were more apt to respond to vagus pressure by depression of conduction than were the hearts of untreated patients. Weil believes that digitalis stimulates the cardio-inhibitory centre and, at the same time, renders the conducting system more susceptible to the influence of the vagi. Fahrenkamp (52) found that in cases of auricular fibrillation pressure over the vagus nerves was sometimes effectual in stopping the ventricles after the administration of digitalis in cases in which

vagus pressure was ineffectual before the drug was given. These findings suggest that the conduction mechanism is rendered more susceptible to vagus action by digitalis, which is in accord with the experimental results of von Tabora (148).

Hirschfelder (80) investigated the action of the drug on dogs in which auricular fibrillation was produced by faradization and found that the irregularly beating ventricles were markedly slowed by digitalis, but the rapid arrhythmia promptly returned when the vagi were paralyzed by atropin. Further slowing was obtained by very large doses of digitalis after atropin had been given and complete heart block with slow ventricular rhythm could be induced. Cushny (31) performed similar experiments with cats and found that after the vagi had been cut, strophanthin failed to remove the irregularity and acceleration of the ventricles until a late phase of the action of the drug set in, with auriculo-ventricular dissociation. He contends, however, that these experiments are not comparable to auricular fibrillation in man in which malnutrition of the cardiac tissues presumably exists.

It has been suggested that digitalis is especially potent in blocking impulses sent down by the fibrillating auricles. In order to determine whether this is true Robinson (127) studied the effect of vagus stimulation in dogs, both with normally beating hearts and with auricular fibrillation induced by faradization of the auricles. The results were recorded by electrocardiograms. The experiments show that the type of auricular activity has no influence on the degree to which impulses are blocked by vagus stimulation. In the light of these experiments it would seem that the character of the auricular activity, whether coördinated or fibrillary, plays no part in the effectiveness of digitalis in depressing conduction by stimulation of the cardo-inhibitory centre.

An examination of the evidence bearing on the question of the manner by which digitalis reduces the ventricular rate in auricular fibrillation must lead to the conclusion that various phases of the subject remain unsettled, and little or nothing is known regarding certain of its aspects. It seems established that the ventricular slowing is brought about by the dual action of digitalis on the cardio-inhibitory centre and directly on the conduction pathway, but the

relative importance of these two effects is not clearly understood. Furthermore, it is not yet determined to what extent cardiac malnutrition or other changes in the heart influence the action of the drug, nor what relation exists between the ventricular slowing in cases of auricular fibrillation produced by bodily rest and that caused by digitalis. A clearer understanding of these problems would doubtless place the use of digitalis in auricular fibrillation on a more intelligent basis, and would probably lead to its more effectual employment.

There is some evidence in favor of the belief that digitalis may be beneficial in cases of auricular fibrillation independent of the ventricular slowing it produces. Edens (37) for instance, has observed clinical improvement without any diminution of the ventricular rate. Increased efficiency of the ventricular contraction by the direct action of the drug on the heart muscles may play some part in its valuable effects in this condition.

Patients with auricular fibrillation are not all equally susceptible to the beneficial effects of digitalis. The cases may be roughly divided into two groups, those in which auricular fibrillation follows the so-called rheumatic infections and those in which arterial sclerosis, with presumably accompanying cardio-sclerosis is present, and frequently with a preceding syphilitic infection. The first group is composed, as a rule, of young or middle aged persons who show very rapid ventricular rates. Cases of this group are, as a rule, those that show the most striking benefit from digitalis. The cases of the second group may be much less benefited. They do not show such high ventricular rates, and, in some cases, it is not above the average normal level, although evidences of heart failure are well defined. Mackenzie (109) who first pointed out this distinction, attributed the difference to changes in the cardiac muscle, and holds that the reaction to digitalis is much more easily induced in cases with presumably slight myocardial damage than in cases with extensive degeneration. This distinction is undoubtedly correct, but it does not take into account the state of the conduction pathway, which is presumably more damaged in the second group of cases than in the first. Digitalis is often of little value in cases in which the ventricular rate is slow before digitalis is given. In these cases, the tissues involved in the

conduction of the cardiac impulse are damaged and are therefore not capable of transmitting impulses at a rapid rate. This damage may be taken as an evidence of a widespread involvement of the myocardium which is unable to maintain an efficient circulation even when the ventricles are contracting slowly. Under these circumstances, further slowing may cause no improvement in the circulation, and sometimes may be distinctly harmful.

On the other hand, in many cases of auricular fibrillation, the myocardium is sufficiently preserved so that the ventricles can maintain the circulation efficiently when their rate is held within bounds by digitalis. Certain conclusions regarding prognosis are justified therefore from the response to the drug. Patients should be studied with this point in mind. Physicians should also learn to distinguish between cases in which excellent results are to be expected from those less liable to benefit, before drawing conclusions as to the efficiency of the preparation of the drug being used.

The ventricular rate, in many cases, can be regulated at will by the amount of digitalis administered. The optimum rate and the doses required to maintain it, must be determined by trial in each case. The dosage has to be varied frequently, and no rule applies to all cases. The proper amount of the drug to be given is to be determined by the effect of various doses on the symptoms of heart failure and by the ventricular rate.

It must be borne in mind that the radial pulse cannot be relied upon for determining ventricular rate, as when the ventricles are beating rapidly and irregularly, many contractions may fail to produce a palpable pulse at the wrist. For this reason the ventricular rate should always be determined by counting the number of heart beats per minute by means of the stethoscope. It is very useful in following the effect of digitalis in auricular fibrillation to determine the number of ventricular contractions that fail to produce a palpable pulsation at the wrist. The number of such beats per minute constitute the so-called pulse-deficit, a term invented by George Draper (personal communication). A pulse deficit of 20, 30 or more a minute is often found in untreated cases, and the disappearance or reduction of the pulse-deficit should be taken as an important guide for the proper dosage of digitalis.

It is usually desirable to reduce the ventricular rate to between 70 and 80 beats per minute, although some cases seem to have a better state of cardiac efficiency when the rate is higher, and Pratt (122) has found that the circulation is sometimes best maintained at a rate much lower than that of the normal heart. In one of his patients under constant administration of digitalis, the heart rate was rarely above 50 per minute during a period of two years.

The constant employment of digitalis is usually necessary to keep the ventricular rate continuously slowed, and the benefits of constant use of digitalis have been pointed out by Schmoll (141), Borultau and Stadelmann (7), Fulton (56), Pardee (117) and others. Pardee has brought out the fact that the body must be kept nearly full of digitalis and not nearly empty, and in order to accomplish this, the drug must be given at a rate comparable to that of its elimination from or destruction in the body. Fulton (56) remarks that many cases need continuous administration of the drug and by the use of small doses the heart may be controlled so that the patient may be able to go on with his ordinary routine of life indefinitely.

It is certainly one of the most gratifying experiences in medical practice to see the great benefit digitalis frequently brings about and maintains in these patients for months and years by its constant administration in doses so regulated that toxic symptoms do not appear, while the heart is kept continually under its influence.

Excessive amounts of digitalis in auricular fibrillation may produce complete heart-block, causing the ventricles to assume a regular rhythm at an excessively slow rate. Taussig (149) has reported two such cases in which permanent complete block developed during digitalis administration. Slow regular ventricular action occurring in cases of auricular fibrillation during digitalis medication should always be taken as an indication of excessive action of the drug and should lead to its discontinuance. Complete heart-block may occur without other evidences of intoxication, as happened in a case reported by Robinson (128).

Another disturbance of the heart beat which is prone to follow the administration of the drug in cases of auricular fibrillation is the so-called bigeminal pulse or coupled rhythm. It may appear when relatively small amounts of the drug have been given, which do not

ordinarily produce toxic symptoms. The absolutely irregular rhythm is replaced by pairs of beats followed by pauses of varying lengths. There is usually a fairly constant time relation between the coupled beats. Coupled rhythm may be detected by the study of the heart sounds and radial pulse as Christian (14) has stated, but electrocardiograms reveal their true nature. Coupled rhythm is produced by the occurrence of a premature contraction of ventricular origin following regularly each ventricular beat stimulated by the auricles. Its occurrence is to be taken as a sign for discontinuing digitalis.

Edens and Huber (38) have studied this phenomenon and consider that it probably only occurs in hypertrophied insufficient hearts. They regard its occurrence with relatively small amounts of digitalis as an unfavorable prognostic sign. They found that coupled rhythm was always dependent on ventricular premature contractions which resulted, they believed, from an increase in the irritability and stimulus formation in the ventricles produced by digitalis in damaged hearts where there was a high calcium content in the blood. The amount of the drug producing coupled rhythm was quite variable.

The beneficial action of the drug on the peripheral circulation in auricular fibrillation has been demonstrated by Stewart and Scott (145) who studied the blood flow in the hands by means of calorimeters. They found that in three of four cases, the blood flow was increased in the hands within twenty-four hours after the tincture of digitalis was given. This finding is merely a quantitative corroboration of the effects of the drug when determined by the clinical study of signs and symptoms of heart failure.

The striking action of the digitalis bodies in slowing the ventricular rate in auricular fibrillation has been put to useful purposes in studying certain aspects of the digitalis problem, as the ventricular slowing usually occurs as a sharply defined reaction on the part of the heart which may be readily distinguished as of digitalis origin, the onset and duration of which can be determined.

b. Auricular flutter is a disturbance of the heart beat caused by an excessively rapid auricular rate, usually about 300 contractions per minute, accompanied by varying degrees of heart-block. Recent studies of Lewis, Feil and Stroud (102) indicate that auricular flutter is in reality closely allied to fibrillation. They interpret the very

rapid auricular activity as dependent upon a continuous circuit of the cardiac impulse through the auricles, along a constant path at a rate constant for each case. They account in this way for the practically absolute regularity of the auricular rhythm which they have demonstrated, and for other features of this cardiac disorder. The ventricles do not participate in the excessive auricular rate, but may respond to every second, third or fourth auricular contraction. Flutter generally persists for months or years, and does not tend to cease spontaneously. The recognition of auricular flutter can be readily accomplished by electrocardiograms and less easily in polygraphic tracings. Without the use of graphic methods, it cannot be distinguished with certainty.

Digitalis has proved of definite value in treating cases of auricular flutter. Lewis (96) first showed conclusively that flutter passed into fibrillation during the administration of the drug, although Mackenzie (108) and Turnbull (150) had previously recorded cases of the same nature. In a later paper, Lewis (97) recorded other instances of this action of digitalis, and has pointed out that when fibrillation surplants flutter it is usually temporary and the normal cardiac rhythm may be resumed permanently. These observations have been frequently confirmed, and Lewis states that the production of fibrillation by digitalis administration is an important therapeutic measure in cases of flutter. The action by which auricular flutter is transformed into fibrillation is uncertain. The drug renders the auricles more liable to fibrillation than before, and this may be accomplished either by direct action on the auricular tissues or by its action through the vagi. It seems possible that the conduction of impulses through the auricles is interfered with and areas of block are produced, a change which is, according to recent investigations, an important factor in the causation of auricular fibrillation. When first set up, fibrillation tends to disappear, and in the cases under discussion the normal rhythm is resumed before fibrillation becomes, so to speak, firmly established. Lewis has shown that auricular flutter may be abolished by the administration of digitalis after it has persisted for months.

Digitalis may serve another useful purpose in auricular flutter as Lewis has also pointed out. With the auricular rate as high as 300 per

minute the ventricles may respond to every second contraction, and so attain a rate of 150 beats per minute. Digitalis by its action on the conduction pathway between auricles and ventricles may increase the degree of heart-block which is already present, presumably because of the excessive auricular rate. After the depression of conduction the ventricles may respond to only every third or fourth auricular contraction and so be decidedly reduced in rate, much to the improvement of the cardiac efficiency. Thorough digitalization of patients with auricular flutter is therefore a valuable procedure whenever this disturbance of the heart beat is encountered.

c. Cardiac contractions of abnormal origin. Impulses leading to cardiac contractions may arise in some point in the auricles or ventricles quite outside the region of the heart in which the normal rhythmical stimuli are generated. Such impulses may arise occasionally or frequently at fairly regular intervals causing the single premature ectopic beat, or extrasystole, or they may arise rhythmically and so rapidly that they dominate the cardiac rhythm causing a high grade of tachycardia. These various conditions dependent upon cardiac contractions of abnormal origin will be discussed separately in their relation to the action of digitalis.

Premature contractions or extrasystoles occur in association with various cardiac disorders, as well as in hearts that show no other abnormalities. They have no material influence on the circulation when occurring only occasionally, but when frequent, as often for instance, as every second or third regular heart beat, they tend to lower the efficiency of the heart, often produce annoying subjective symptoms and are therefore undesirable. There are two questions that arise concerning the relation of digitalis to premature contractions. Has the drug any effect in preventing their occurrence and is their spontaneous occurrence a contraindication to the therapeutic use of the drug?

It has long been known that large doses cause premature contractions which are recognized as one of the most constant manifestations of the influence of the drug on the heart, and as such have been discussed previously. Although Wenckebach (155) was aware of this effect of large doses, he reported several cases, and published curves of two of them in which small doses of digitalis caused the disappearance

of premature contractions after they had been present over long periods of time. He considered this effect as due to the direct action of the drug on the heart muscle. Mackenzie (109) has given digitalis to patients in whom spontaneous premature contractions of ventricular origin were occurring and was unable to observe any effect on them.

Edens (37) has perhaps studied the subject more closely than any one else. He reports the results of the use of digitalis in a variety of cases with premature contractions, and he has attempted to differentiate these cases on the basis of the possible causation of the premature beats. He concludes that premature contractions dependent upon recent rheumatic lesions of the heart are not influenced while those that appear to be associated with insufficiency of the coronary circulation are probably cleared up by digitalis. He found that the type of premature contractions that occur in persons who use tobacco excessively, the so-called nicotine extrasystoles, are not affected by the drug, and those occurring in nervous persons sometimes disappeared and sometimes were unaffected by digitalis. Edens considered that the variable effects are dependent upon the fact that there are different forms of premature contractions and that sharp differentiation on the ground of further experience is urgently needed. He considers that premature contractions should be taken as contraindications for the intravenous use of digitalis.

So little is known regarding the underlying causes of ectopic premature contractions that a satisfactory hypothesis regarding the means by which digitalis may effect them and the manner in which they may respond to the drug cannot be put forward. It is possible that the heart muscle may be rendered less irritable by the stimulation of the cardio-inhibitory centre, as Wenckebach (155) has suggested. The production of premature contractions by the direct action of the drug probably occurs in hearts not already disposed to them only after very large doses, approximately 50 per cent of the minimum lethal dose. It is possible therefore that this action does not come into play even in hearts showing spontaneous premature contractions, while other effects of the drug tend to cause their disappearance. Their presence should not be taken as a contraindication for the therapeutic dose of digitalis, although it should lead to caution, and

should indicate a reduction of dosage. The favorable influence of digitalis in bringing about the disappearance of premature beats is not to be viewed with any great expectations of success, although in small doses it may have this effect in some cases. Christian (19) has stated that

> this question of the exact relation of digitalis to extrasystoles is one still under discussion. In most cases, extrasystoles are more an incident in, rather than a cause of cardiac decompensation and their presence can be neglected in considering the probable efficiency of digitalis therapy.

d. Paroxysmal tachycardia has been shown by electrocardiographic studies to be a disturbance of the heart beat dependent upon the mechanism closely allied to that responsible for the occurrence of single premature contractions. It is characterized by the sudden onset of a very rapid cardiac rate, usually between 150 and 250 beats per minute, which terminates as suddenly as it begins, the rate usually returning to normal after a period of some hours or days. Very short paroxysms are also seen. These periods of tachycardia are apt to recur, once they have been established. The tachycardia is brought about by the production of cardiac impulses in some point removed from the region of normal impulse formation. The ectopic focus generates impulses at an abnormally rapid rate, and assumes the rôle of cardiac pace-maker. The ectopic focus is usually in one of the auricles but ventricular foci have also been found to produce such paroxysms.

Digitalis has proved to be without influence on the high rate of the heart brought about by this disturbance of its mechanism. Edens (37) has reported a case in which the paroxysm stopped during digitalis administration, but the relation of cause and effect cannot be established. During the attack the degree of heart failure varies greatly from patient to patient; but, in most instances, when the attacks are not prolonged, the evidence of cardiac insufficiency is not marked. Individuals who have these paroxysms of tachycardia not infrequently show no definite evidence of heart disease between attacks, and have, presumably, hearts that can adjust themselves to the abnormal rate. In prolonged attacks, however, the heart may show signs of muscular fatigue, which may be considered as an indi-

cation for the use of digitalis. Robinson and Hermann (133) have recently reported a case of prolonged tachycardia of ventricular origin in which digitalis was given without any beneficial effects.

e. Heart-block. The depression of conduction is one of the most definite effects which digitalis produces, as has already been brought out. Therefore in partial heart-block, when further interference with the passage of the cardiac impulses from auricles to ventricles is decidedly undesirable, digitalis is contraindicated.

Cases are occasionally seen in which the conduction time is lengthened on account of faulty nutrition of the functional tissues between the auricles and ventricles. This depression in conduction is comparable to that which occurs during asphyxia, and may disappear with an improvement in the state of the circulation. In these cases digitalis has been observed to bring about an improvement in the auriculo-ventricular conduction, and to shorten the conduction time to within normal limits. Careful study by those experienced in abnormal cardiac physiology is necessary to differentiate these cases from those showing depression of conduction produced by structural changes in the conducting system.

In complete heart-block, when the ventricular contractions are being stimulated by the inherent rhythmicity of the ventricles, the action of the drug on conduction may be disregarded. Under these conditions an improvement of the efficiency of the ventricles and especially the quickening of their slow rate is the result to be desired, and there is evidence to show that this may sometimes be attained by digitalis.

Jagic (82) noted improvement of a patient with complete heart block when small doses of digitalis (0.05 gram per day) were given. Martinet (110) has also advocated the use of digitalis in complete heart-block, and has warned against its use when the block is partial. He believes that digitalis acts both on the vagi and directly on the heart muscle, and he points out that the latter action may be effectual in complete heart-block while the independently beating ventricles are not under the control of the vagi, and so the former action can be disregarded. Bachmann (3) has studied a case in which strophanthus was given with beneficial results and with an increase in the ventricular rate while the auricles were slowed. Bachmann (4)

reported a second case with similar results, in which the ventricular rate increased from 23 to 31 beats per minute during the administration of the drug. He is of the opinion that strophanthus is of more benefit in complete heart-block than digitalis.

Hewlett and Barringer (79) report a case in which digitalis produced auriculo-ventricular dissociation and in which the ventricular rate exceeded that of the auricles. They suggest on the basis of this observation that the drug may be of value in complete heart-block. They failed, however, in the one case that afforded them an opportunity of testing their hypothesis to get any increase in the ventricular rate following the administration of digitalis.

Cushny (29) has suggested that helleborein might be especially useful in heart-block, as he says it has an effect on the heart muscle similar to that of digitalis, but is without effect on the cardio-inhibitory mechanism. Recent investigation of cases of complete heart-block have shown that the rate of the independently beating ventricles is, in most instances, free from the control of the vagi, and therefore the inhibitory action of digitalis should not be considered of moment in these cases. The direct action of the drug on the heart muscle may be advantageous in increasing the output of the heart even without a change in rate. Complete heart-block is not a contra-indication for digitalis according to Mackenzie (108) but the drug should be withheld in cases of temporary heart-block where a return of the normal heart beat is anticipated.

3. Heart failure with normal cardiac mechanism

a. Myocardial insufficiency is the name now frequently applied to that form of heart disease in which the power of the heart muscle is apparently impaired, and in which no other cause can be discovered to account for the failure of the heart to maintain the circulation adequately. The term myocarditis has been used to express the same condition, but myocardial insufficiency is to be preferred, as it expresses functional rather than structural damage of the heart. In many instances, no satisfactory explanation can be found by the present day methods of examination of tissues for obvious myocardial inefficiency on the basis of structural changes in the heart muscle.

In the case under consideration, ample evidence of heart failure is present, while there is no conspicuous disturbance of the cardiac mechanism, no demonstrable structural damage to the valves, no alterations in the vascular system sufficient alone to account for the symptoms. The patients, who are usually past middle life, are short of breath, unable to lie flat in bed and often have anginal pain, especially on exertion. They frequently have edema and cyanosis, evidence of congestion of the lungs and liver, with hydrothorax and, at times, ascites.

The heart is enlarged and the character of the heart sounds may be altered. There is often a systolic murmur at the apex. The urine usually contains albumen and casts, and there may be other evidence of renal insufficiency. The blood pressure is frequently elevated and the heart rate is often increased.

The clinical picture may vary considerably and only the most obvious symptoms have been enumerated in order to define this frequently encountered condition. The value of digitalis in the type of myocardial insufficiency that has been described is not nearly so well established as it is in cases of heart failure with auricular fibrillation. This is to be expected, as heart failure in these cases is dependent upon some fundamental change in the cardiac muscle which no known means can remove; while in auricular fibrillation a definite factor of heart failure can be altered advantageously. The difference in the effects of digitalis in these two types of heart disease is noted consistently in the literature on digitalis since it was first brought out by Mackenzie (108) in 1905, and since these types have received definite clinical differentiation.

The prime object in the use of digitalis in myocardial insufficiency is to improve the ability of the heart in propelling the blood and in restoring the balance between the arterial and the venous side of the circulation. It has already been shown how difficult it is to obtain any definite direct evidence of changes in the output of the heart. Various elaborate methods have been devised for its indirect determination, but these have not been extensively used in the study of the problem now under consideration. It is necessary therefore to rely on the improvement of symptoms by digitalis, and this evidence is often difficult to evaluate.

It has been repeatedly shown by Cushny (29), Mackenzie (109), Edens (37), Pongs (120), Cohn (20), Pratt (122), Christian (16) and others that the cardiac rates of these cases is usually not slowed by digitalis, and the action of the drug on the cardio-inhibitory mechanism apparently plays as a rule no part in the favorable results which the drug may accomplish in cases with regularly beating hearts. Cohn (20) has emphasized the importance of differentiating cases with edema from those without it, and there is general agreement that in cases of myocardial insufficiency with edema, diuresis follows the administration of digitalis, the edema is diminished or disappears and there is a general improvement in symptoms. At the same time, the idea prevails, as recently stated by Eggleston (47) that the diuretic action of the drug is essentially secondary to its capacity to relieve heart failure and to restore the circulation. Diuresis must be looked upon, if this idea is correct, as evidence of a beneficial influence of the drug on the heart muscle, although this conclusion is not as yet warranted as final. This question has already been discussed.

The various statements of those who have studied properly the effect of digitalis in myocardial insufficiency indicate that benefit is often derived from its use, but the manner of its action is still obscure. Cushny (29) noted improvement in such symptoms as dyspnea, cyanosis and edema without any change in the cardiac rate, and attributed the improvement to the direct action of the drug on the heart muscle. Edens (37) also observed clinical improvement without slowing of the heart rate, and he believes the contractility of the heart is effected favorably by digitalis, but considers that myocardial damage limits its influence in this regard. Cushny's (31) later work emphasizes the relation of malnutrition of the heart to the action of the drug, and he believes the drug is more likely to act directly on the heart when malnutrition is present. Mackenzie (109) has always been skeptical regarding the idea that heart failure may be relieved by the effect of the drug on the heart muscle. Christian (15) in discussing what he terms chronic myocarditis says that it constitutes a group of cases in which digitalis is very effective, whether auricular fibrillation is present or not, but with recurrences of heart failure the drug becomes less and less able to bring relief. Windle (162) has also observed definite improvement in the cases under

discussion, but says that the improvement in advanced cardiac failure is often only temporary, and the drug becomes less and less effective as the cardiac inefficiency advances. Christian (16) has recently reported a series of cases of myocardial insufficiency with regularly beating hearts and with edema in which digitalis produced satisfactory effects.

Pratt (122) has employed strophanthin intravenously in these cases, and says that as improvement has occurred in forms of heart failure that are rarely, if ever, relieved by digitalis, it is suggested at least that strophanthin given intravenously exerts an effect on the contractility or tonicity of the heart muscle that is not obtained from digitalis in therapeutic doses. West and Pratt (156) have recently remarked that there is little doubt in the minds of most clinicians that much good can be expected from proper dosage in patients showing regular rhythm, when their symptoms are evidence of heart failure. They gave full doses of dried aqueous extract of digitalis to a number of such patients and in many obtained effects that were quite as gratifying as in those showing auricular fibrillation.

The heart is often unusually susceptible to digitalis in the class of cases under consideration, and toxic effects may be produced by relatively small doses, so that careful study of these cases is especially necessary when digitalis is administered. It is evident that digitalis is of definite value in cases of heart failure dependent upon myocardial insufficiency, especially when edema is present. The manner in which the drug acts is still a matter of uncertainty. The fact that abnormalities exist in the heart which have not as yet been closely duplicated in animals renders comparison with experimental results unwarranted. The influence of digitalis in cases of myocardial insufficiency needs further study.

b. Pulsus alternans, a phenomenon dependent upon myocardial weakness, consists of an alternation in the regularly beating heart of relatively strong and weak cardiac contractions which gives an alternating character to the radial pulse. This abnormality of the cardiac contractions is a grave sign of myocardial insufficiency. It has been observed following the administration of digitalis, apparently as an effect of the drug; and as such it has already been considered as a toxic effect. Questions have been raised as to whether the

presence of pulsus alternans is a contraindication for the use of digitalis and what effect the drug has upon it when already present. Windle (162) has made an extensive study of these questions. He considers pulsus alternans as being invariably the expression of an overtaxed heart, and says that it is the only form of pulse rhythm giving definite information regarding the functional efficiency of the heart. Windle was among the first to demonstrate the fact that the presence of pulsus alternans is to be considered a sign of impending death, even when circulatory failure is not extreme. He has studied the effect of digitalis in over 100 cases of heart failure showing alternation, and although the condition does rarely follow the administration of the drug, he never found that digitalis increased the alternation of the pulse or produced harmful effects when it was present. On the contrary the alternation and irregularity in rhythm of the pulse frequently became lessened, and not seldom was abolished. The presence of high blood pressure does not contraindicate the use of the drug in these cases. Windle points out the relation of rate to alternation, and shows that as the diastolic periods of cardiac rest lengthen, the tendency to alternation of contractions diminishes. On the other hand, the slower the rate at which alternation is observed, the more serious is the prognostic significance, as the more extensive exhaustion of the heart muscle is indicated. Pulsus alternans may disappear permanently under digitalis in cases of myocardial damage following rheumatism, but Windle believes it practically never permanently disappears in aged patients. Christian (14) who publishes some excellent records of pulsus alternans, has obtained good results in patients showing this phenomenon. He reports a case in which digitalis produced striking slowing with definite clinical improvement, but without disappearance of alternation. Christian remarks that it is to be remembered

> that a pulsus alternans is a sign of a very much impaired myocardium, and when the myocardium is greatly impaired the likelihood of functional improvement from digitalis is much decreased. To push digitalis in such a case may do much damage. Here it is particularly difficult to judge how far to carry digitalis therapy if no evident effect is produced. It would seem that in many of these cases the margin between no therapeutic effect and a serious toxic effect is a very narrow one.

Windle, in the light of an extensive experience, advises, on the other hand, to continue the drug until vomiting or coupled rhythm occurs.

4. Valvular heart disease

Valvular heart disease as such is not an indication for the employment of digitalis. Much misconception has been prevalent in medical practice regarding this fact. On the other hand, many cases with structural changes in the valves are much benefited by digitalis when heart failure follows or accompanies valvular defects. No one can conceive that the condition of the valves can be altered by the drug, and the presence of a valvular murmur, even when it is dependent upon a structural change in a valve, is never to be taken as a reason for giving digitalis. Experimental destruction of one or more of the heart valves in animals is not followed, as a rule, by marked disturbances of the circulation. However, under these conditions, the heart is otherwise undamaged, and is able to compensate for the faulty valves.

In patients with valvular disease the myocardium and the coronary arteries are likely to participate in the damage that has affected the valves, and share in the causation of heart failure. Various disturbances of the heart may therefore occur when valvular disease is present, and these disturbances rather than those of the valves should serve as an indication for the use of the drug. This is the attitude expressed by all students of the drug who have considered this matter, but it has not been discussed in the recent literature, because no doubt it has appeared self-evident.

One possible benefit of digitalis in valvular heart disease has, however, been recently suggested by Cohn and Fraser (22). They point out that a delay in the conduction of the cardiac impulse from auricles to ventricles may be of advantage to the heart when mitral stenosis is present, as such an effect would increase the time available for the left auricle to empty itself before the onset of ventricular contraction. They suggest that the action of digitalis in bringing about this delay of conduction may be a factor in its beneficial effect in cases of mitral stenosis, and that by the proper regulation of dosage, the conduction time may be constantly lengthened. No observations bearing directly on this suggestion have as yet appeared.

One form of valvular disease, aortic regurgitation, has gained the reputation of being a contraindication for digitalis. This tradition no doubt goes back to the original description of the lesion by Corrigan (27) in 1832, for there he says that digitalis lengthens diastole and so allows more blood to regurgitate through the incompetent valve. All of his patients with this lesion who received the drug seemed to have become worse from its action. Corrigan does not state, however, that the heart rate can be slowed by digitalis. Christian (16) has commented on this subject and says:

> There still lingers the tradition that aortic insufficiency contraindicates digitalis, because digitalis would prolong diastole and the large regurgitant flow of the blood under these conditions would stop the heart in diastolic paralysis; a good enough theory; only it seems to have no basis in fact.

Pratt (121) also states that this lesion is not a contraindication for the use of digitalis, and this has been the general experience of all who have paid particular attention to this subject.

It may be said therefore that in determining the indications for the use of digitalis, valvular lesions as such should be ignored, and other evidences of cardiac disorder should always serve as the guides for the use of digitalis in valvular heart disease. However, the suggestion of Cohn and Fraser (22) concerning the possible value of the drug in mitral stenosis is worthy of consideration and careful study.

5. Disturbances of the nervous mechanism

Certain disorders of the heart are encountered in which without any disturbance of the cardiac mechanism, the heart assumes an abnormally rapid rate. The underlying cause of these disorders is not well understood, but the more prominent symptoms seem to be dependent upon a functional derangement of the nervous mechanism controlling the heart, and are perhaps caused by an overbalancing of the inhibitory nerves, the vagi, by the accelerators. Two examples of such disorders seem worthy of consideration: the so called effort syndrome or neuro-circulatory asthenia, and hyper-throidism, since digitalis has been employed in the hope of lessening the tachycardia in each instance.

a. The effort syndrome is a condition which has come into prominence during the years of the recent war. It seems to be particularly prone to occur in young men of military age under emotional stress and strain incident to war, and affects probably those whose nervous make-up renders them predisposed. The chief symptoms consist of palpitation of the heart with tachycardia, breathlessness and cardiac pain on exertion, and manifestations of a disturbed nervous system, such as headache, giddiness and disturbed sleep. The symptom complex serves as a good example of what is generally called a cardiac neurosis, and because the more prominent symptoms are referable to the heart, digitalis has been used, especially with the idea of overcoming the tachycardia. Parkinson (119) has reported a study of the effects of digitalis on these cases carried on at the English Heart Hospital at Colchester, which was under the direction of Sir Thomas Lewis. Parkinson's results and conclusions serve as an example of the general experience with the use of digitalis in this condition. He administered full doses of the drug to a series of 20 patients. The heart rate was reduced but little, and the increase of rate which occurred with exercise or with standing was not controlled, to any appreciable extent, by digitalis. There was no effect on either the systolic or diastolic blood pressure. Parkinson states that digitalis scarcely influences this group of patients, even when the pulse is rapid, and he concludes that it is not indicated in the condition known as effort syndrome or neuro-circulatory asthenia.

b. Hyperthyroidism or exophthalmic goitre serves as another example of tachycardia which is primarily independent of any anatomical lesion of the heart or of any alteration in the mechanism of the heart beat. Several possible causes present themselves. The toxic substance generated by the thyroid gland may act directly on the heart or its nervous mechanism, producing the characteristic acceleration of rate; or there may be some fundamental change in the nervous system which manifests itself in part by causing tachycardia; or the increased cardiac rate may be secondary to the generalized increase in metabolic processes of the body. Without a better understanding of this subject, no rational therapy directed at the heart alone can be devised. Digitalis has been used with the hope of slowing the heart rate; but, as Cohn (20), Fulton (56) and others have pointed out, always without success.

It may be said that not only in the two examples of cardiac neuroses that have been considered, but in all types of disturbances of the nervous mechanism, digitalis fails to produce any beneficial effects. The tachycardia, usually the most prominent symptom, is not influenced by the drug. Whenever the diagnosis can be established with certainty, if should be considered unwise to use digitalis in the cardiac neuroses with any expectation of obtaining beneficial results.

X. DIGITALIS IN INFECTIOUS DISEASES

1. Fever in relation to the action of digitalis

During the course of severe infections, the possibility of heart failure is naturally constantly before the physician. Digitalis has been used both as a preventive measure with the idea of "supporting" the heart through a period of unusual strain and also as a curative measure when signs of heart failure have appeared as a complication of an infectious disease. In this connection, the relation of fever to the action of the drug has been a matter of discussion. Cohn and Jamieson (24) have reviewed this subject and state that definite differences of opinion exist among American, English and German clinicians. Some consider the drug is without power in the presence of fever; while it has been used extensively by others, especially in pneumonia. Mackenzie (109) states that digitalis has little effect upon the heart rate when it is elevated by agents which increase its excitability, and cites the effect of fever as an example. Cushny (30) also says that digitalis is especially apt to be inefficient when fever is present.

Cloetta (19), however, has recently recommended the use of digitalis in acute infections, combined with camphor and believes that it is important to begin the administration early in the course of acute infections. His recommendations are apparently based on somewhat empirical reasons however.

The relation of the body temperature to the action of digitalis has been subjected to animal experimentation. According to Jamieson (83), Gunn studied the effect of strophanthin on the perfused heart at temperatures ranging from 28° to 41°C. and found that the drug acted more quickly at higher temperatures. Recently Hirschfelder,

Bicek, Kucera and Hanson (81) have studied the effect of high temperature on the action and toxicity of digitalis. They injected the tincture intravenously into cats, the body temperatures of which were elevated by immersion in water, heated to 43° to 46°C. They found that digitalis produced effects in these animals similar to those observed in normal animals, but there was a decided influence on the minimal lethal dose per kilo of body weight which is shown in the following table.

TEMPERATURE	AVERAGE LETHAL DOSE
°C.	*cc. per kilogram*
37–39	0.94
41	0.78
42	0.59
43	0.375

On the basis of these results Hirschfelder and his collaborators warn against giving large doses of the drug to patients with high temperatures.

2. Pneumonia

Pneumonia is the infectious disease in which digitalis has been most extensively used, and in which its action has been especially studied. These studies furnish valuable information regarding the action of digitalis in the presence of fever.

Fulton (56) in 1914 expressed the general opinion prevalent at that time regarding the employment of the drug in pneumonia.

> Where there is cyanosis with low blood pressure and a rapid, feeble pulse, the question always arises whether digitalis should be administered. The evidence in regard to its value in such cases is not satisfactory. It is not likely to do harm unless there is some involvement which might encourage the formation of heart-block, in which instance it should not be used.

Since this time, Cohn and Jamieson (24) have carried out a systematic study of the action of the drug in pneumonia, and have obtained results that give definite answers to the questions involved. They studied a series of 105 cases of pneumonia, 49 of which received digitalis, while 56 cases served as controls and were studied with

equal care. Electrocardiograms were obtained at frequent intervals, and particular attention was paid to the length of the conduction time, variations in the T wave of the electrocardiogram and the ventricular rate in cases of auricular fibrillation.

Digitalis was given by mouth in the form of digipuratum. They state:

> In general the criteria we employed permitted us to judge satisfactorily whether digiatlis was acting. We found that the signs appeared after the same amount had been given and following the same length of time in which these signs appeared in non-febrile cases originally studied. When no digitalis was given the signs did not appear.

Cohn and Jamieson conclude that digitalis acts during the febrile period, and produces a beneficial, possibly a life-saving effect when auricular fibrillation or flutter occurs during the course of pneumonia. Whatever beneficial action digitalis has on the function of the normally beating non-febrile heart may be expected from its use in the febrile heart in pneumonia.

Cohn (21) observed auricular fibrillation or flutter in 12 out of 123 cases of pneumonia; or in practically 10 per cent. He considers the frequency of these cardiac derangements in pneumonia sufficient ground for keeping patients under the influence of digitalis during the course of this disease. The drug was consequently routinely administered to pneumonia patients according to the following plan, the dose being indicated in grams of the leaf.

	DAY OF DISEASE								
	1	2	3	4	5	6	7	8	9
If seen early	0.5	0.5			0.5	0.5			
If seen late				1.0		0.5	0.5		

Stone, Phillips and Bliss (146) studied the effect of digitalis in a large series of cases of pneumonia in an army hospital during the recent war. They attempted to digitalize thoroughly the cases during the first forty-eight hours in the hospital by administering 0.17 cc. of a standardized tincture per pound of body weight in several large doses. The total amounts ranged from 20 to 30 cc.

With these doses vomiting occurred in only 4 to 5 cases; partial heart-block appeared in one, and there was a considerable rise of blood pressure in another. There were 871 cases in their series and the administration of the drug was begun at a certain date after about half the number of cases had been seen. The conditions under which these patients were observed did not allow detailed study but there was a striking difference in the death rate after the use of digitalis was begun. This is shown in the following table:

	BEFORE THE USE OF DIGITALIS	AFTER THE USE OF DIGITALIS
	per cent	*per cent*
Deaths not associated with sepsis	25.8	11.8
Deaths from uncomplicated pneumonia	17.1	11.2
Deaths from pneumonia complicating measles	46.3	14.8

Stone and his co-workers believe the tincture of digitalis was responsible for the decrease in the percentage of deaths in the cases not associated with empyema or other "septic" conditions, being definitely valuable in the type of cases whose deaths are associated with cardiac failure.

Caution must be exercised in drawing sweeping conclusions from this study, as under the circumstances, it cannot take into account certain possibilities such as variations in the virulence of the infecting organisms or other conditions altering the severity of the infections.

Jamieson (83) carried out an investigation on the action of the lethal dose of strophanthin in normal animals and in animals with experimental pneumonia. Cats and dogs were used and strophanthin was given by intravenous injections. Pneumonia was produced by intratracheal insufflation. Jamieson studied the effect of strophanthin in 21 cats that were not given pneumonia and 12 animals were studied that had pneumonia but were not given strophanthin. The action of the drug was studied in a large series of infected animals. The results of these experiments led to the following conclusions:

1. When a like amount of strophanthin is injected intravenously, the mortality is the same in both normal cats and in cats suffering from experimental pneumonia.

2. The minimal lethal dose is the same in normal dogs and in dogs suffering from experimental pneumonia.

3. The presence of an acute infection in these animals does not interfere with the action of strophanthin on the heart.

4. Electrocardiographic changes occurring in the heart's action when strophanthin is injected are found to be similar in normal and in infected animals.

5. The identity of strophanthin action in infected and in normal animals renders it probable that a like similarity may be anticipated in man, under normal conditions and in pneumonia.

This work corroborates the idea expressed by Cohn and Jamieson that the action of digitalis is the same in pneumonia as it is under non-febrile conditions. Probably the unfavorable influence of fever on the action of digitalis arose from the observations that the drug failed to slow the heart in febrile conditions, but it is now known that the drug usually fails to slow the normally beating heart when fever is not present except under special and rare conditions. Further work is necessary to substantiate the idea that digitalis "supports" the heart during pneumonia, although the work of Stone, Phillips and Bliss is suggestive and Cohn considers it desirable to give the drug to patients with the disease in anticipation of auricular fibrillation. The question may be raised, however, as to whether such use of digitalis may not tend to bring on auricular fibrillation in these cases.

3. Diphtheria

Diphtheria is another infection which deserves special consideration because of the frequency of cardiac damage as one of its most severe complications. The view has been held for a long time that the drug does not benefit the cardiac disorders following diphtheria and is possibly harmful in this condition. Only recently, however, has this matter been subjected to careful study by modern methods. McCulloch (111) after an extensive study of the heart in diphtheria by means of the electrocardiograph, and after many careful observations on the effect of digitalis in children, has drawn attention to the close similarity between the cardiac disturbances produced by diphtheria and the toxic effects of digitalis on the heart. In diph-

theria presumably through the action of the toxin on the heart, conduction is often damaged, premature contractions frequently occur, or there may be striking changes in rate, either a high grade of tachycardia or marked slowing. McCulloch attributes the slowing of the heart in diphtheria to vagus stimulation, and he has studied the effect which atropin has upon it. This interpretation is perhaps open to question. There is, however, such a close resemblance between the effects on the heart of diphtheria toxin and of digitalis that it seems to be adding insult to injury to administer the drug to patients with the cardiac complications of diphtheria. McCulloch's paper is a valuable contribution to the knowledge of indications for the use of digitalis.

XI. DOSAGE OF DIGITALIS

1. Oral administration

a. The amount of the drug. Withering laid down a sound principle for determining the proper dosage of digitalis when he wrote, "Let the medicine be continued until it either acts on the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects." He recognized the necessity of regulating the dose of the drug by its action, rather than by accepting a standard dose as applicable for various samples of the drug and for various types of disease in which it might be employed. In spite of his directions, standards of dosage of wide variations have been advocated.

Eggleston (42) states that the doses of the tincture of digitalis recommended by recognized authorities range from 2 minims (less than $\frac{1}{4}$ gram of the leaf) three times a day to 30 minims (3 grains of the leaf) three times a day; the larger dose being fifteen times as great as the smaller. Hatcher and Bailey (72) have discussed the use of the tincture of strophanthus and strophanthin, and have drawn attention to the great diversity of opinion regarding the dosage of these drugs, and to the apparent confusion relative to the activity of various preparations. It seems probable that variability of absorption is largely responsible for the lack of uniformity of dosage, as will be brought out later. It is apparent that many misconceptions have existed regarding the dosage of digitalis and its allies.

There has been recently a tendency to attribute poor results of digitalis to its use in inadequate doses.

During the past few years considerable attention has been focused on the matter of dosage, and much progress has been made towards establishing sound principles, based on accurate determinations in the laboratory and in the clinic. Eggleston and Hatcher deserve a large share of the credit for this progress, and their contributions to various phases of the subject have proved of much value.

The fundamental problem involved in the dosage of digitalis is the determination of the average amount of standard preparations required to produce maximum therapeutic results in the types of patients to whom the drug is usually given and which does not produce severe toxic symptoms. The method that has recently come into use is essentially the same in principle as that advocated by Withering, and consists in the administration of the drug to series of patients until well defined evidence of digitalis action appears. Modern methods, however, allow the detection of specific effects of the drug with greater precision and at an earlier stage than was possible in Withering's day.

After the determination of the average amount of the drug necessary to produce the desired effects in a series of patients, attempts have been made to convert this finding into a rule designed to allow others to employ the drug in the amount most likely to benefit similar patients, and to allow its use under conditions which do not permit the determination of the early evidences of its toxic action.

Following such carefully conducted studies as those of Mackenzie (109), recommendations as to dosage were made which reflected the results obtained in each series of patients. All of the students who employed accurate methods for the detection of digitalis action advocated larger doses than had been previously customary, but the earlier students of the present period of accurate objective clinical observation pointed out the fact that the dose must not only be fairly large but also that the drug must be continuously administered until definite effects were produced, when it should be either discontinued or much reduced in amount.

The study of Eggleston (42) marks the beginning of much progress in digitalis dosage. His paper published in 1915 brought out a

number of points of permanent value, and is an excellent example of clinical observation based on a sound training in the pharmacological laboratory. Eggleston undertook to determine whether or not it was possible to establish the dose of digitalis for man on the basis of the activity of the drug as determined by a biological assay. He studied, at the same time, several other problems directly concerned in the question of the dosage of digitalis and its allies and pure principles. These problems were:

1. The rate, degree and uniformity of the absorption of the crude drug and its active principles.
2. The influence of sex, age and weight on the dose.
3. The influence of the preparation-infusion, tincture, etc., on the dose.
4. The influence of the cardiac condition.
5. The influence of the size of the daily dose on the total dose required.

Eggleston used tinctures and infusions of digitalis, made from leaves of different sources and varying in activity, and crystalline digitoxin dissolved in 70 per cent alcohol or made into tablet triturates. The activity of each preparation was determined in terms of cat units by the method of Hatcher and Brody (74). These drugs were administered by mouth to a series of patients, some of whom had auricular fibrillation. Care was taken that none of the patients had received any one of the digitalis group of drugs within a period of not less than three weeks prior to the beginning of the observation. The patients were kept under observation in bed for from three to seven days before digitalis or digitoxin was given, whenever their condition justified such a period without medication. Body weight, intake and output of fluids, blood pressure, polygraphic—and in some instances—electrocardiographic records were obtained as indicated, as well as frequent physical examinations. Personal bias was, as far as possible, eliminated in judging changes in the condition of the patients.

The study was carried out on 47 patients, 6 of whom had two courses of treatment, making 53 in all. Fifteen studies were made on cases with auricular fibrillation and 38 on non-fibrillation cases.

The action of digitalis was determined by subjective and objective improvement in the symptoms and signs of heart failure and in the appearance of minor toxic effects. The phenomena included in this latter category were marked sinus arrhythmia, partial heart-block, premature contractions, nausea and vomiting.

The details of the method used by Eggleston are given because his work is a good example of the methods of clinical studies which have yielded valuable results, and indicate the various procedures necessary to prevent faulty observation and false conclusions when studying the effect of these drugs on patients.

The most important feature of Eggleston's study is that it enabled him to determine the amounts of the drugs in terms of cat units per pound of body weight required to produce therapeutic and toxic effects. In other words, he introduced two quantitative factors into the consideration of dosage that had previously received only indefinite consideration, and had not been brought into accurate relation with each other. Eggleston brought to the problem of dosage drugs of known activity and measured their effects in terms of the total amount used in relation to the weight of the individuals receiving them.

No definite difference was found between the amounts of the drugs necessary to produce comparable therapeutic or minor toxic effects in cases with auricular fibrillation and in non-fibrillation cases.

Eggleston draws the following conclusions and deductions from his studies:

1. The cat method of standardization of digitalis yields results on which the dose for man can be based.

2. The average therapeutic dose of digitalis given orally to man in the form of tincture is 0.146 cc. of an average high grade tincture per pound of body weight as established by thirty-three observations.

3. Fifteen observations have established 0.066 cat unit, or 0.023 mgm., per pound as the average therapeutic dose of crystalline digitoxin.

4. Approximately half of a total of 48 courses of administration of either digitalis or digitoxin, full therapeutic effects were secured with doses falling within 15 per cent above or below the average dose.

5. Doses considerably larger than the average were taken in 17 instances without the production of more than mild toxic symptoms.

6. The activity of the preparation of digitalis has no material influence on the dose required in terms of cat units.

7. Age, sex and cardiac condition do not seem to influence the size of the dose required.

8. Both digitalis and digitoxin are probably rapidly and fairly uniformly absorbed from the alimentary canal of man, but digitalis is less completely absorbed than is digitoxin.

9. Strophanthus, the strophanthins, ouabain, true digitalin, and some other digitalis substances are poorly or irregularly absorbed when given by mouth to man or to the higher animals and are unsuited for therapeutic use in this way.

Eggleston has pointed out the practical application of his results. In dealing with the tincture of digitalis, the dose may be taken for convenience as 0.15 cat unit per pound of body weight when the tincture possesses a strength of 1 cc. to the cat unit. This has been found to be the average strength of high grade tinctures and represents 100 mgm. of the crude drug. This strength may be accepted as a basis for the calculation of the total amount probably necessary to produce the maximum therapeutic results. A patient weighing 150 pounds would therefore require 22.5 cc. of such a tincture. Eggleston states:

> On the basis of the patient's actual or estimated weight, the total amount which would probably be required should be calculated and this quantity could then be divided into single or daily doses according to the rapidity with which it was desired to induce the full therapeutic effects. If, after the total calculated amount had been taken, the patient failed to show the full therapeutic effect or some minor toxic action indicated that enough had been given, the administration should be continued in small repeated doses until one or the other of these evidences called for its withdrawal.
>
> In this way it is possible to give a third to half of the total calculated therapeutic dose at a single administration, to follow this in from four to six hours with a quarter to a third of the total dose, and to give the remainder in a few doses of smaller size at intervals of from four to six hours. By this plan of administration, the full effects can be secured in from twelve to thirty-six hours in the majority of cases.

The administration of half of the total dose may call for the giving of from 5 to 15 cc. of the tincture at once, and it might be feared that such a large dose might cause gastric irritation and nausea or vomiting. I have given such doses repeatedly since the completion of the greater portion of this work and have never seen the least disturbance of any kind arising as a consequence. This is due to the fact that the nausea and vomiting following the administration of the digitalis bodies is of central origin and results only after the absorption of a sufficient quantity of the drug into the circulation.

It should be reiterated in this place that the use of such large doses of either digitalis or digitoxin as are mentioned is not a safe procedure unless the patient can be under nearly constant observation and unless the effects of the treatment can be graphically recorded at frequent intervals. This practically limits such procedures to hospital practice and to those well versed in the significance of polygraphic and electrocardiographic records.

Certain precautions necessary in using digitoxin according to the calculations he describes are pointed out.

Eggleston (45) has recently published a brief description of his plan for administration of digitalis by the body-weight method, and has given simple formulas for the determination of the dose of the leaf, the tincture and the infusion when the weight of the patient and cat unit strength of the drug is known. The average relative strength of these forms of the drug have been found by Hatcher and Eggleston to be

100 mgm. of the leaf = 1 cat unit
1 cc. of the tincture = 1 cat unit
10 cc. of the infusion = 1 cat unit

When the activity of a particular specimen given is not known, it is safe to use these figures for purposes of calculation; but then only 75 per cent of the calculated dose should be given in order to allow for the possibility of excessive activity of the specimen.

He recommends differentiating urgent and non-urgent cases, and points out the importance of reducing the dose when any member of the digitalis group has been taken in the preceding ten days, particularly when evidences of partial digitalization are present. Eggleston also prescribed certain safeguards which should be carefully followed. The signs of minor digitalis intoxication, such as nausea

and vomiting, reduction of the heart rate below 60 per minute, and the appearance of frequent premature beats; of definite heart-block; of marked phasic arrhythmia, or of coupled rhythm are to be taken as indications for the cessation of further administration. By the Eggleston method the calculated total amount of the drug may be given to urgent cases in twenty-four or thirty-six hours. By giving an initial dose of the drug consisting of one-third to one-half of the total calculated amount, and then by giving smaller parts of it at six-hour intervals, over-dosage is prevented as digitalis action becomes evident in six hours when the drug is given by mouth.

Eggleston comments on this method of administration as follows:

> The employment of this method of administration of digitalis is without danger to the patient if the directions are followed in detail and if the safeguards are carefully observed. By its employment it is usually possible to produce maximal digitalis action in from twelve to eighteen hours, and marked therapeutic effects are frequently observed within six hours after the initial dose. By its use, it is possible to dispense with the intravenous or intramuscular administration of ouabain, amorphous strophanthin, or other digitalis body in the great majority of cases of heart failure.

The demonstration of the necessity for using digitalis and its allies according to its activity as determined by biological assay is one of the most important results of Eggleston's work, and for that reason, the question of biological assay was taken up quite fully in the earlier part of the review. The relative strength of the various members of the digitalis group were also taken up, and the figures given in that portion of the review may be taken for the determination of dosage for their oral administration. However, the problem of absorption from the gastro-intestinal tract must always be borne in mind, and it will be brought out presently that this has a striking influence on the action of various drugs and preparations when administered orally.

Emphasis should be given to the work of Hatcher (68) on the persistence of the action of the digitalins in connection with dosage. He showed by animal experiments that all the digitalis bodies are synergistic and that the action of one is added to that of another. For this reason, the effect of any drug of this group contraindicates

the administration of any other of the digitalis bodies. Warning is gravely expressed by Cohn (21) that

> digitalis should, under no circumstances, be given to a patient who has previously been given digitalis in any form or by any route. The failure to obey this warning has, on many occasions, been followed by disastrous results to the patient.

The actual amount of digitalis in terms of the powdered leaf which is usually required to produce the maximum therapeutic results for an average adult weighing about 150 pounds is, according to Eggleston's calculations, 2.25 grams. Mackenzie (109) states that 5 to 8 drachms of the tincture usually produces the desired effects in his cases, an amount which should equal 2 to 3.2 grams of the crude drug. Cohn (20) found that slowing of the heart rate in cases of auricular fibrillation occurred after from 2 to 2.8 grams of the leaf had been given, and Cohn and Fraser (22) found that when the digitalis was administered as the tincture or as digipuratum, a disturbance of the rhythm was usually effected when an equivalent of from 2 to 4 grams of the leaves had been given, although symptoms of intoxication usually appeared before half of this quantity was given.

West and Pratt (156) using a dried aqueous extract of digitalis obtained satisfactory therapeutic effects with a preparation having a cat unit strength of 0.1 gram when from 1.4 to 2.2 grams had been given, while Cohn and Levy (25), obtained the desired therapeutic results when 1 gram of digipuratum of the same activity was given.

White and Morris (159) and Kay (88) have confirmed Eggleston's principles of dosage. Robinson (130) has also administered a standardized tincture in large single doses, calculated according to Eggleston's formula, to 100 cases of heart disease; the doses ranging, as a rule, from 15 to 25 cc. or 15 to 25 cat units, the amount being regulated by the body weight. He observed excellent therapeutic results without encountering any serious toxic effects. He found that the use of large single doses is apparently not dangerous under proper conditions of study, and brings the heart rapidly under the influence of the drug.

Pardee (118) has published the results of a study of sixteen patients to whom the tincture was administered. His results also closely

confirm the findings of Eggleston. He found wide variations similar to those seen by Eggleston which occur in the amount of the drug required by different individuals to produce the same effects, the variations in his series being from 36 per cent below to 50 per cent above average.

When digitalis is being administered in liquid form it should always be remembered that there is a great difference between the amount contained in a drop and in a minim. Cloetta (19), Pratt (121) Christian (16), Pardee (118), and others have referred to the inadequacy of dosage which has resulted from considering a drop equal to a minim, while in reality, according to Pratt, 1 cc. or 15 minims of the tincture contains 35 to 40 drops when the ordinary medicine dropper is used.

In summing up the work of these several students of digitalis dosage, it may be concluded that the average total amount of the drug necessary to produce therapeutic effects when administered orally has been firmly established, provided the activity of the preparation and the body weight of the patient are taken into consideration. This average total amount may be given in large single doses under proper conditions and when certain precautions are carefully followed, or it may be given in relatively small doses, at regular intervals provided doses are sufficiently large to allow the drug to accumulate in the body and are not below the rate of elimination of the drug, a matter to be considered later.

Pardee (118a) in his second paper on digitalis dosage expresses the opinion that when a tincture of unknown strength is being used, it is safe to follow the rule of giving 1 minim for each pound of body weight in a single dose when the effects of the drug are desired rapidly. This dose is well under the calculated maximun dose of Eggleston, and allows for a considerable increase in the strength of the tincture above that of the average preparation.

The question of applying the body-weight method to children has recently been investigated by McCulloch and Rupe (112). They observed the amounts of the tincture of digitalis necessary to produce definite effects in 36 children varying from one to fifteen years, none of whom had heart disease. Frequent electrocardiograms were obtained and the usual methods of clinical observation were carried

out. McCulloch and Rupe give the weight of the children in kilograms, but for purpose of comparison with the work already reviewed, it will be given here approximately in pounds, two pounds being allowed for each kilogram. The weights of the children ranged from 17 to 100 pounds.

The tincture employed was standardized at frequent intervals and had continuously a strength of approximately 1 cc. per cat unit. It was found to produce therapeutic effects in adults when given in doses of 0.15 cc. per pound of body weight. In normal children considering the group as a whole, from two to five times as much digitalis per pound of body weight was necessary to produce recognized digitalis effects as was found necessary to produce an optimum therapeutic effect in adult patients with heart disease. The difference of children in this regard was especially true for those weighing over 40 pounds. There were 12 such cases in the series, 8 of whom showed no response to doses of 0.29 to 0.48 cc. per pound, while the other 4 required from 0.62 to 0.87 per pound of body weight before showing evidence of the action of the drug.

Among the 24 children weighing less than 40 pounds, 14 responded to less than 0.5 cc. per pound while 8 required from 0.5 to 0.87 cc. per pound.

Two children aged twelve and twenty-one months respectively weighing 19 pounds each did not respond to the drug until 19.2 cc. had been given in 24 doses, requiring approximately 1 cc. per pound of body weight before showing evidence of digitalis action. The total amount of the tincture was given in this series in from 5 to 24 doses, being administered 4 times a day. Elimination therefore probably had little or no influence on the total amount taken, although of course absorption is a factor difficult to evaluate.

McCulloch and Rupe conclude that children weighing from 16 to 40 pounds, or up to about the age of four years, respond more readily as a rule to digitalis, than do those above this weight and age while the older children required a distinctly larger amount per unit of body weight than is required to produce comparable effects in adults with heart disease. Considerable variation in the amount of the tincture necessary to bring about a response in the hearts of the children was found, but it is evident that relatively large doses of digitalis

can be administered to children with comparative impunity. McCullock and Rupe (112a) have studied a second series composed of children with heart disease. In this series they found no qualitative difference in the effect of digitalis when compared to the action of the drug on adults. They found, however, that children with heart disease require about 50 per cent more of the drug per pound of body weight on an average than do adults to obtain the same results. Some of the cases required 100 per cent more of the drug, that is a quantity double the estimated dose, while others required only 10 per cent additional amount.

b. Absorption of digitalis from the alimentary tract is a problem which has an important bearing on the dosage of the drug when administered by mouth, and has recently received considerable attention. The relative rates of absorption of the various members of the digitalis group, variations in absorption of a single preparation and influences delaying absorption have been studied both in the laboratory and in the clinic.

Schmiedeberg (139) states that the active principles of digitalis, digitoxin, digitalin and digitalein are slowly absorbed from the gastrointestinal tract.

Ogawa (116) called attention to the delay in the time required for digitalis to affect the heart when given by mouth as compared with the time required after intravenous injection. He concluded that the slowness of absorption is the greatest factor in the "latent period" of digitalis action. He states that digitoxin is not absorbed from the stomach and only with relative slowness from the intestines. He found that by examining the withdrawn gastric contents that different preparations of digitalis have different rates of absorption, and that digitoxin for which he applied a colorimetric test, remains for a shorter period in the stomach when taken as digipuratum than when taken as powdered leaves or as the infusion.

Ogawa is of the opinion that the absorption of the digitalis bodies is further delayed by congestion of the abdominal vessels, as he found that experimental obstruction to the portal circulation prevented their absorption. Cloetta (19) also considers that congestion of the intestinal vessels and of the liver interferes with the absorption of digitalis. Eggleston (42) on the other hand, states that prompt and

efficient absorption of digitalis and digitoxin seems to take place even in the face of considerable abnormality of the alimentary canal, for patients manifesting evidence of marked congestion of this region, resulting even in repeated vomiting, respond quite as promptly and to the same doses as do those who are apparently free from disturbance.

Haskell, McCants and Gardner (66) studied the relative rate of absorption of various digitalis bodies from the gastro-intestinal tract of animals. They determined the amount of digitalis intravenously injected necessary to produce emesis after constant amounts had been given orally, and took as the measure of absorption from the gastro-intestinal trace the size of the intravenous dose necessary to produce this result, as the larger the amount absorbed from the gastro-intestinal tract, the less is needed by vein. They found that the tincture of digitalis was much better absorbed than the infusion, and that the expensive preparations, digipuratum, digalen and digipoten had no advantages over the tincture in regard to absorbability.

The most important work that has been done on the matter of absorption is that from the laboratory of Hatcher and from the clinic of Eggleston. Their numerous papers contain many references to this matter. Hatcher and Baily (61) called attention to the fact that the tincture of strophanthus is poorly absorbed from the gastro-intestinal tract, and Eggleston has recently stated in discussing the work of White, Balboni and Viko (158) which has already been referred to, that the tincture of squill owes its relative inactivity to its poor absorption. Hatcher and Bailey (73) have also pointed out that dangerous variations in absorption of strophanthus may take place. Eggleston (47) has recently summarized his ideas regarding the use of members of the group other than digitalis as follows:

> The materia medica of the digitalis group of drugs is large, but digitalis alone is well absorbed from the alimentary tract of man. Strophanthus, convallaria, squills, etc., are alike poorly absorbed and irregularly absorbed. Strophanthus deserves special mention, because it is 100 times as active as digitalis, yet the official dose is only half that of digitalis, and it is often given in equal doses. The irregularity of its absorption is of greater importance than the fact that its absorption is generally poor, for in some cases, serious poisoning has resulted from the rapid absorption of the customary dose. We are convinced that strophanthus should never be

used for oral administration to man on account of the danger of serious accident, despite the fact that it often has been so used with satisfactory results.

J. T. Halsey (62) has expressed similar views regarding the oral administration of strophanthus, and contends earnestly that the poor and irregular absorbability of strophanthus from the alimentary canal should prohibit its use by mouth.

Recent interest has centered largely on the absorbability of the tincture of digitalis, the most widely used form of the drug. Many references are found in the older literature regarding the slow absorption of the drug in any form, but the recent clinical studies furnish definite facts regarding the absorption of digitalis from the gastro-intestinal tract in man. Eggleston (47) states that the absorption of a single dose of a high grade tincture is apparently completed in six hours and he quotes the results of Pardee and of Levy, both of whom obtained electrocardiographic evidence of digitalis action in from two to four hours after the drug was given by mouth. Robinson (129) administered large single doses to 26 patients with auricular fibrillation and observed the onset of ventricular slowing constantly in from 2 to 5 hour after the administration of the drug. These findings indicate that with the tincture he used a fairly rapid and uniform rate of absorption took place from the alimentary tract.

Pardee (118a) has studied the rate of absorption of digitalis from the gastro-intestinal tract. He gave the drug in the form of the tincture in doses determined by allowing 1 minim for each pound of body weight, and administered this amount in a single dose. He then followed the action of the drug in frequently taken electrocardiograms, noting especially variations in the T wave and in the heart rate. Changes in the T waves indicative of digitalis action were observed within two hours of taking the drug in three of nine patients, while within three hours, these changes were observed in seven of the nine patients. Pardee's observations are confirmatory of those of Robinson, although the doses used by the former were considerably smaller. Pardee considers that the variation in the size of the dose within certain limits does not appear to have a marked influence on the time of onset of the digitalis action.

Eggleston (42), has compared the absorption of the tincture of digitalis with that of digitoxin, digitalin and digitalein. The last two substances are so poorly absorbed from the alimentary canal as to render them unsuitable for therapeutic use, while the absorption of digitoxin is slightly less rapid than that of the tincture.

Attention has been directed recently, however, to marked variations in dosage required to produce well defined digitalis action when tinctures carefully assayed by the cat method were used. Wedd (152) found that in one patient 100 cc. of a standardized tincture produced no effect while six months later definite digitalis action followed the administration of 35 cc. of another equally active tincture. Of the first tincture 280 cc. were given to another patient during a period of ten weeks and produced no clinical symptoms. He found that from 24 to 34 cc. of the first tincture were required to cause inversion of the T wave of the electrocardiogram while it occurred with 10 cc. or less of the second equally active tincture. Wedd attributes this difference in the action of the two tinctures to variations in absorption, and says that it is evident that biological standardization is no guarantee of the clinical efficiency of a given preparation of the drug.

A similar experience occurred to Oppenheimer (quoted by Eggleston (46)), who gave 5 to 9 times the usual dose of the tincture without evidences of either therapeutic or toxic action. Although individual susceptibility may play some rôle in producing these marked discrepancies, the variations in absorption seem to be the prime factor.

Hatcher (71) has taken cognizance of these variations in digitalis action, the frequency of which is not yet known, and has investigated them. He says that

> Certain of the digitalis principles are readily absorbable from the gastrointestinal tract of man, as well as that of animals, while others are absorbed much less readily, and it seems probable that the failures just mentioned arose from the fact that preparations contained relatively large proportions of the less readily absorbable active principles.

Hatcher has found that the more readily absorbable principles are soluble in chloroform, and he describes a method for separating the chloroform soluble from the chloroform-insoluble principles. He has

obtained a chloroform-soluble substance resembling somewhat digitoxin, both chemically and pharmacologically. It may be dissolved in alcohol and is miscible with water without precipitation. The resulting weak alcoholic solution has been found to undergo little change during a period of a year since it has been under observation. This preparation seems to exert the typical cardiac action of digitalis, and has all its other advantages.

The clinical use and especially the absorbability by patients of this preparation has been studied by Eggleston (46) who has published some preliminary observations. He shows the marked uniformity of absorption of the chloroform-soluble extract of digitalis prepared from a variety of different leaves. This uniformity contrasts sharply with the variations noted in the use of certain tinctures from a variety of sources.

The chloroform-soluble extract is shown to be absorbed at least as rapidly as the best tincture of digitalis, and its persistence of action is apparently of the same order as that of digitalis of the best grade. The observations indicate that for oral administration the chloroform-soluble extract is not superior to a well absorbed tincture of digitalis, but it is far superior to tinctures which are derived from a variety of sources, the absorption of which shows very marked variations when individual specimens are compared. The chloroform-insoluble extract is very poorly absorbed from the human alimentary tract as well as from that of the cat.

It is evident that absorption must be taken into more strict account than it has been in the past in determining the efficiency of a digitalis preparation, and means must be devised if possible to determine its absorbability as well as its activity in the standardization of the digitalis intended for oral administration.

The effect of the gastro-intestinal secretions on the digitalis bodies is a problem closely allied to that of absorption. Ogawa (116) studied this problem in animals and in man, and found that strophanthin was destroyed by the gastric ferments, just as Holste (quoted by Ogawa) concluded that the pancreatic secretion destroyed digitalin. Ogawa's study revealed, however, that the glucosides of the digitoxin fraction are resistant for several hours to the juices of the gastro-intestinal tract.

Cloetta (19) has investigated the effect of gastric juice on digitalis in vitro, his digalen preparation being subjected to shaking for one hour at 38°C. with varying percentages of hydrochloric acid. The percentage of the drug destroyed was then determined and the following results were obtained:

with 22 per cent HCL	100 per cent digalen destroyed
with 12 per cent HCL	60 per cent digalen destroyed
with 4 per cent HCL	40 per cent digalen destroyed
with 3 per cent HCL	35 per cent digalen destroyed
with 2.5 per cent HCL	35 per cent digalen destroyed
with 1.5 per cent HCL	25 per cent digalen destroyed

Cloetta considers that a "nerve poison" is generated by the action of hydrochloric acid on digitalis, the therapeutic properties of which are destroyed. He recommends giving the drug when the stomach is empty, and giving it with an alkaline mineral water, weak tea or a mucilage. He also believes that his findings indicate the usefulness of giving digitalis by rectum, which he advocates. Further study of these subjects is needed before they can be adopted as principles influencing the therapeutic use of digitalis.

The problem of the decomposition of various digitalis bodies by acids and digestive ferments has been discussed by Hatcher and Eggleston (78) in their studies in elimination, and a review of a number of experimental studies of this subject is given, including that of Holste quoted by Ogawa. Following their analysis of these various investigations, they say that there is no convincing evidence that any of the digestive juices or their ferments have any important destructive action on any of the digitalis glucosides following their therapeutic administration by the mouth.

c. The speed of action or time elapsing between the oral administration of digitalis and the appearance of its effects is also a matter on which absorption has an important bearing. The fact that digitalis requires many hours or even days to affect the heart when given in the customary doses has been perhaps the chief disadvantage in the use of the drug in cases of heart disease in which prompt action is urgently indicated.

Cushny has stated that one great limitation in the use of digitalis is caused by the slowness with which its action is elicited. "Rarely

is any distinct change to be seen before the fourth day of treatment, and this precludes its use in the most acute cases." (Quoted by Eggleston (42)). Recent clinical studies have shown, however, that it is the size of the dose rather than the delay in the absorption or in the action of the digitalis that is the most important factor in regulating the speed of action of the drug. It is necessary for a certain amount of the drug to be present in the body before the action appears, and the action appears much more quickly with large than with small doses, several or many of which are needed to supply the amount of the drug necessary to exert its action. It has been the time required for the accumulation of a sufficient amount of digitalis that has become largely responsible for the ideas regarding the very slow speed at which the drug exerts its action.

Eggleston (42) has shown the relation between dosage and speed of action for digitalis and digitoxin, large doses of the digitalis bodies becoming active on an average in 13 hours; small doses in thirty-eight hours while large doses of digitoxin required fifteen hours to produce their earliest effect, and smaller doses required forty-two hours. He demonstrates that both these drugs when given in large doses can induce full therapeutic effects within comparatively few hours after the administration of the first dose.

Robinson (129) has investigated the question of the rapidity of the action of digitalis by giving the full calculated amount of the tincture in a single dose to patients with auricular fibrillation. In a series of patients in whom digitalis caused a striking reduction of the ventricular rate, he found that ventricular slowing (or disappearance of auricular flutter) began in from two to five hours, in all of the 16 cases where the initial effect was observed, and that maximum slowing in 26 cases occurred in from six to twenty-six hours. As only one dose was given in most of these cases, the question of the accumulation of the drug played no part.

These results have been confirmed by Eggleston (46) and by Pardee (118a), who found that two or three hours after a single large dose of the tincture slight changes in the T wave of the electrocardiogram characteristic of digitalis action usually appeared. Eggleston also quotes Scott as having obtained digitalis effects in from one to two hours by the administration of 10 cc. of the chloroform-soluble extract of digitalis given in a single dose.

Cohn and Levy (25) have compared the speed of action of comparable doses of digitalis (digipuratum) when given by mouth and g-strophanthin when injected intravenously. An effect with digitalis has been observed in a little more than two hours, while the speed of action is often faster with strophanthin than with digitalis, though when strophanthin is given in divided doses it may require nearly two hours to obtain an effect. In other instances, an effect may be obtained, as is well known, in twenty minutes or less.

This matter of speed of action of digitalis has been recently summed up in a vigorous way by Hatcher (70).

> It is necessary to call attention again to the difference between an immediate action and immediate effect, because it has long been taught, without a particle of real evidence, that the action of digitalis cannot be induced promptly. The whole range of digitalis action up to the maximum, that is, cardiac stoppage, can be induced in from five to fifteen seconds by the intravenous injection of digitalis tincture deprived of its alcohol, or digitoxin. This simple experiment disposes forever of the mischievous claim that digitalis action is slow. The *effect* of therapeutic doses is *gradually* induced; the action is *immediate*. A bullet fired through the heart *acts* instantaneously; the *effect* is a fatal hemorrhage, the rapidity of which depends largely on the size of the wound. With suitable dosage, digitalis exerts its action in much less time than was formerly believed to be possible.

2. Intravenous administration

The value of the intravenous administration of ouabain, strophanthin, and some other principles of this group is generally recognized, and it is considered a life-saving measure because of the promptness with which the action of these drugs can be obtained in urgent cases of heart failure. In emergencies, however, the cause of heart failure may be difficult to determine and when it occurs under such conditions as during a surgical operation, its cause is often incorrectly attributed to "cardiac dilatation," as Levine has recently pointed out. The use of large doses of digitalis by mouth and the prompt action which usually results makes the use of these drugs by intravenous injections rarely necessary. It must always be employed with caution, as has been pointed out in discussing fatalities following its use, and intravenous injections should never be given to

patients who have been receiving full doses of the digitalis bodies in any form.

Digalen, the so called soluble digitoxin, prepared by Cloetta (17) is the first form of digitalis recommended for intravenous employment. Edens (36) was among the first to report favorable results with the intravenous administration of this drug, and he emphasizes especially the rapid action thus obtained, and the fact that the drug can be used in cases where absorption from the gastro-intestinal tract would probably be distinctly faulty. He considers its use not without danger, however, and recommends its use by slow injection in desperate cases. Cloetta (19) has recently expressed his belief in the intravenous use of digalen as the ideal method of giving digitalis.

Strophanthin was introduced as a drug for intravenous administration by Fraenkel, and its use is fully discussed by Fraenkel and Schwartz (54). They recommended a dose of 1 mgm. ($\frac{1}{67}$ of a grain) but say it should not be given more often than once a day. Agassiz (2), studied the effect of intravenous injections of strophanthin on a series of cases of auricular fibrillation and recommends doses of $\frac{1}{250}$ to $\frac{1}{300}$ grain repeated several times every one to three hours for several doses. Ventricular slowing usually resulted from one injection. It may appear as early as half an hour after the injection, but the ventricular rate may continue to be further slowed during the following twenty-four hours. Two or three injections are usually sufficient to produce the normal ventricular rate in 4 to 9 hours. Strophanthin employed intravenously seemed to possess action quite similar to the other members of the digitalis series. Agassiz found the most suitable method of administration to consist in the injection of $\frac{1}{250}$ grain repeated after three hours, and followed after a further interval of three hours by an injection of $\frac{1}{300}$ grain if required. The injection may be followed by pain at the site of injection and by a rise of temperature. In one instance, a patient died unexpectedly some twelve hours after the injection had ceased, but the relation of cause and effect was not definitely established.

Fulton (156) reports a case of auricular fibrillation treated by intravenous strophanthin in which the pulse reduced from 144 to 34 within a period of about twenty-four hours, after two doses had been given, the first of $\frac{1}{250}$ of a grain and the second of $\frac{1}{150}$ of a grain.

The condition of the patient passed quickly from one of extreme discomfort with dyspnea and restlessness to a condition of perfect comfort.

Such observations as those of Agassiz and Fulton indicate that doses of 1 mgm. ($\frac{1}{60}$ grain) as advocated by Fraenkel are too large, and fatal accidents have resulted from the use of strophanthin in such doses, as has been brought out when digitalis fatalities were discussed. However, the work of Levine and Cunningham (94) indicates that it is no more dangerous than digitalis intravenously administered when the so-called margin of safety is considered, the average difference between the minimum lethal dose and the minimum toxic dose being 48 per cent in each instance. They have also found that various digitalis preparations act as quickly on the heart when injected into the veins as does strophanthin. They observed toxic effects two minutes after the intravenous injection of digitalis and cardiac standstill in sixteen minutes. All effects produced by either digitalis or strophanthin were seen to occur within six minutes after the injections.

Levine (92) has suggested a fractional method of intravenous injection of strophanthin on the basis of his experimental studies of the action of the drug on the living cat's heart. He points out that numerous fatalities have resulted from the intravenous administration of strophanthin, but most of them have occurred when the drug was given to patients who recently had taken digitalis, or when large doses were repeated on the same day. His experiments show that it is practically impossible to foretell the toxic dose for patients but they indicate that a "margin of safety" exists between the minimum lethal dose and the minimum toxic dose. Levine recommends that strophanthin be injected in several fractions of the desired dose, a half hour intervening between the fractions, during which time, the signs of intoxication are watched for. This procedure will prevent giving more than one fraction, say 0.1 mgm. in excess of the amount necessary to produce the earliest toxic signs. Electrocardiograms are very useful in showing premature beats or changes in the P-R interval as a result of the drug. This procedure should certainly diminish or avoid the dangers of the drug. According to Levine, Vaquez and Lutembacher have reported almost 2000 intravenous injections of ouabain without harm or fatality.

Danielopolu (34a) has also recently stated that strophanthin can be safely given only in small doses, and recommends the use of 0.25 mgm. intravenously two or three times a day. This he calls the method of fractional doses, and says that by observing the patient carefully before each dose, the drug can be given to patients with extreme myocardial derangement or with kidney disease, which are to be taken as contraindications when larger doses are employed.

Cohn and Levy (25) report that the g-strophanthin which they have used in their comparison with digitalis had an average cat unit of 0.104 mgm. and was given usually in two doses at an interval of one hour—the first of from 0.4 to 0.5 mgm., and the second from 0.3 to 0.5 mgm. No serious untoward effects were observed after these doses.

The drug produced premature beats and ventricular ectopic tachycardia in 52 per cent of the cases of auricular fibrillation and 12.5 per cent of the cases with normal hearts. These toxic effects always appeared within twenty minutes after the injection causing them and disappeared within eight hours. Nausea and vomiting were noted in 10 per cent of the cases. Comparable doses of digitalis by mouth caused undesirable effects in a much smaller percentage.

An important indication for the intravenous use of a digitalis body is persistent vomiting which may be associated with heart-failure as, under such circumstances, it may be impossible to administer the drug orally. Under these circumstances, strophanthin had best be used, for although other digitalis bodies have been employed intravenously, they have not as yet been placed upon as sound a basis for this purpose as strophanthin.

3. Subcutaneous and intramuscular administration

Subcutaneous and intramuscular administration has not proved desirable, and it has not been employed in any of the recent studies of digitalis. Several preparations have been recommended as suitable for subcutaneous and especially intramuscular injections, but all are decidedly painful and apt to cause necrosis, and their dosage has not been accurately determined. Hatcher and Eggleston state emphatically as a conclusion from their studies on the absorption of drugs in general that no rule can be formulated for the calculation of the ap-

propriate dose by one mode of administration from the dose by any other mode of administration. Such determination can be made only be experiment.

4. Rectal administration

Rectal administration has been recommended by Eichhorst (49) in the treatment of chronic myocardial insufficiency. He described several cases which were not benefited by the usual drugs and which did not respond favorably to three powders a day composed of 0.1 gram of powdered digitalis, 1 gram of diuretin and 0.5 gram of saccharin. These cases showed beneficial results from small daily enemata containing 10 drops digalen (Cloetta), 10 drops of the tincture of strophanthus, 0.3 gram of theocin and 5 cc. of lukewarm water. This prescription was injected daily into the bowel and retained. Eichhorst has continued their use over periods of years without difficulty. Five to ten drops of the tincture of opium is added when there is pain or difficulty in retaining the enemata. Eichhorst states that very striking results were obtained by the use of such enemata.

Cloetta (19), has commented upon Eichhorst's results, and he is favorably disposed toward the method. He believes that one advantage of rectal administration is that it does not subject the drug to the action of the gastric juice, which his experiments indicate may destroy it. He believes the favorable results that have been reported are accounted for also by the fact that some of the veins leading from the rectum, the inferior and part of the middle hemorrhoidal veins, empty directly into the inferior vena cava, and do not send the blood through the liver. Because of this, some of the drug introduced into the rectum would probably reach the heart without going through the liver, where it may be destroyed.

The rectal administration has not been extensively used, but it deserves further study, and more should be known regarding the action of the digitalis bodies when introduced into the body by this route.

XII. PERSISTENCE OF ACTION

It has long been known that the action of digitalis persists after the drug is discontinued. Withering (163) recognized this fact in regard to nausea and vomiting, and recommended that the drug be stopped as soon as its activity became manifest, inferring that its beneficial effects persist thereafter. A number of problems are involved in the persistence of action of digitalis. Absorption, fixation by the tissues and especially the destruction or elimination of the drug from the body, may all play some part in determining the continued action of the drug, and as there is but little known regarding any of these matters, no satisfactory explanation of the fundamental problem can be offered.

A number of clinical observations have been made with exact objective methods which show the length of time patients remain under the influence of the drug after full digitalization has been accomplished and the drug withdrawn. Bastedo (5) observed the continuation of digitalis heart-block for three and a half weeks after the withdrawal of the drug. Cohn (20) found by means of electrocardiograms that delayed conduction always persisted for two days in relatively healthy hearts and exceptionally for two weeks after the discontinuance of digitalis, while Cohn, Fraser and Jamieson (23) observed the persistence of the T wave changes in the electrocardiogram for from five to twenty-two days after the drug was stopped.

Eggleston (39) has studied the relative duration of various cardiac manifestations of digitalis action in fifteen cases of his own and from the literature. Coupled beats persisted from four to twelve days, heart block three to six days, combined phenomena six days, auricular fibrillation three days, extrasystoles and sinus arrhythmia two days. Conclusions regarding the relation of digitalis and the disappearance of transient auricular fibrillation is hardly justified.

Robinson (129) followed the ventricular rate of a number of cases of auricular fibrillation after it has been slowed by large single doses of the tincture of digitalis. In twelve cases which were carefully controlled, the ventricular rate began to accelerate in from four to fifteen days after the administration of the dose of digitalis which had caused marked slowing. This acceleration was taken as evidence

that the heart had ceased to be under the action of the drug. The drug was active on an average, for nine days and six hours in these cases. Kay (88) has reported ventricular slowing in auricular fibrillation for from three to five days after doses of digitalis given by the "Eggleston method."

It is evident that various manifestations of digitalis action persist after the drug is withdrawn for from two to twelve days in most cases, but may persist for three weeks or more.

The action of strophanthin when administered by vein has been found by Agassiz (2) to retard the rate of the ventricles of cases of auricular fibrillation for two or three days, when acceleration begins, and the original rate, present before treatment, is seen again in about one week.

Cohn and Levy (25) have compared the persistence of action of digitalis (digipuratum) and g-strophanthin given in comparable doses to cases of auricular fibrillation and found that while the digitalis effect endures usually beyond ten days, and has lasted as long as twenty-three days, it is rare for strophanthin to keep the ventricular rate low for more than five days. It did so once for nine days, however.

A question closely allied with the persistence of action is the so called *cumulative action* of digitalis. Eggleston (39) has discussed the term "cumulative," which is a very loose one. It is generally taken to express the development of signs of action during the administration of small repeated doses of a drug which are much more marked than those caused by a single small dose. Toxic symptoms are usually implied. Accepting this definition, the cumulative action in the case of digitalis is simply the result of a summation of amounts absorbed and active in the body when the intake of the drug is greater than its elimination. The continued use of small doses of the drug raises by the process of summation, the total amount of the drug active in the body, and perhaps fixed by the heart or the nervous tissues to such a point that toxic symptoms develop. When the persistence of action of digitalis is borne in mind the fear of its so called cumulative action can be put aside.

Hatcher (68) has investigated the persistence of the digitalins by means of animal experiments, especially with the hope of throwing

some light on the cumulative action of the drug, which generally means, he says, action which is manifested rather suddenly after the continued use of doses which singly do not cause perceptible effects. The method he employed was as follows: The fatal dose of the digitalis body for a given species was determined in a series of experiments. After toxic, but sublethal doses of the drug had been given, the animals were kept under observation for periods of one to thirty days, and then the percentage of the standard fatal dose required to kill in a characteristic way was determined. The decrease in the amount necessary to produce a fatal result was taken to represent the amount of the drug remaining in the body of the animal. Hatcher and Brody (74) had previously shown that the various digitalis bodies are synergistic, and that ouabain was capable of replacing the various digitalins in the estimation of the fatal dose, and this drug was generally employed for the second injection. Cats were found to be the most useful laboratory animal for this purpose. The many experiments will not be reviewed. Certain conclusions are of importance from the point of view of the therapeutic use of digitalis. Hatcher says that the production of the phenomena commonly called "cumulative action" of the digatalins depends on the relationships existing among a number of factors, including absorption, elimination, and persistence of action, all of which are in need of investigation. The use of the term cumulation tends to perpetuate a misconception. The action of the digitalis persists for periods of time which vary widely with different members of the group, the action of digitalis and digitoxin persisting much longer than those of the other digitalins in common use. The cardiac action of a single very large intravenous dose of digitalis or digitoxin may persist for a full month in the cat, while similar doses of digitalin, ouabain or strophanthus persist for only a day or at most a few days.

Careful regulation of the therapeutic dosage of the digitalins is necessary in order to avoid accidents. This is especially necessary when they are used in such a way that the action is elicited promptly during the period when the action of a previously used digitalin persists, and in this connection it must be remembered that every digitalin is a synergist of every other member of the group.

XIII. ELIMINATION OF DIGITALIS

Little is known and relatively little has been thought apparently regarding the matter of the ultimate fate of digitalis in the body, its destruction and its elimination. It is a matter of real importance, however, in the therapeutic employment of digitalis, when frequent doses of the drug are being given, and especially when it is desirable to keep a patient constantly under the influence of the drug without producing toxic symptoms. This is apparent from the foregoing discussion of the "cumulative action" of the drugs of the digitalis group.

Schmoll (141) recommends that 0.1 gram of digitalis be given daily to heart cases in order to take advantage of what he calls the tonic use of the drug, and he says this dose causes no toxic effects because it is the amount of the drug which can be excreted daily.

The rate of disappearance from the body has been the subject of a clinical investigation by Pardee (118). He points out that when digitalis is given for the purpose of keeping a patient constantly under its influence, improper dosage makes the patient liable to pass gradually out from under the influence when too small a dose is given, or with over-administration, leads to toxic symptoms. As animal experiments cannot give a definite answer as to the rate of disappearance of the drug from the human body, Pardee investigated the question directly in patients by the following method. The tincture of digitalis was given until mild toxic symptoms appeared, when it was stopped entirely for a number of days. It was then given again until the same toxic symptoms reappeared. The difference between the amount of the drug used in the second and in the first course, divided by the number of days between the two toxic points, is taken to indicate the daily average amount of the drug that had disappeared from the body in the interval. It is assumed that there is no change in the patient's tolerance for the drug, a fair assumption in the light of the results with repeated courses in the same patients. The initial doses were so arranged that toxic symptoms appeared in from two to six or eight days; while the second course was usually complete in an average of five days, although it was sometimes prolonged.

Vomiting was the usual toxic symptom employed. Twenty-two tests were carried out on 16 cases, all of whom had a rather marked degree of heart failure before the initial course, but were in better condition when the second course was given. A standardized tincture having a strength of 1.25 cc. per cat unit was used.

The method employed by Pardee showed an average daily rate of disappearance of the drug from the body of 22 minims of the tincture. In half the cases the amount was below and in half above the average, the maximum variations being from 55 per cent below to 82 per cent above. The results of this investigation resemble other work on digitalis in the variability of figures, but in 18 of the 22 tests, the results lay between 12.3 and 30.6 minims per day; while in eleven tests, half of the total, it was between 13.3 and 27 minims, the latter a total variation of only 62 per cent. Pardee says:

> It is evident from this that the average figure of 22 minims per day would afford a fairly satisfactory basis for long continued digitalis medication, since in only half of the cases would it be much more or much less than the patient's ability to dispose of the drug. These results demonstrate the reason for the approximate efficiency of a dose of ten minims of the tincture twice a day, which has commonly been considered sufficient to maintain constantly the digitalis effect. They also demonstrate a new phase of the variability from one individual to another, in the action of digitalis, a variability in the rate of disappearance from the body.

It is interesting that Schmoll's figure of 0.1 gram of digitalis which is equal to about 15 minims of the tincture recommended a number of years ago, should approximate Pardee's figure fairly closely. The importance of this subject warrants its further clinical investigation.

Hatcher and Eggleston (78) have recently published extensive studies in the elimination of certain of the digitalis bodies from the animal organism. Their review of the literature shows that the subject is in an unsatisfactory state. Their studies deal mostly with the elimination of various pure digitalis bodies in the rat, while the elimination of ouabain in the cat and dog was also investigated.

Ouabain disappears rapidly from the blood following injection, and seems to be taken up by the liver where it is apparently decomposed.

Both destruction in the body and elimination by the kidneys probably occur. Many points regarding the elimination of the digitalis bodies remain to be settled, and this work of Hatcher and Eggleston does not appear to present any facts which can be applied directly to the therapeutic use of digitalis.

XIV. PREPARATIONS OF DIGITALIS AND ITS ALLIES

The number of digitalis preparations is very great and they have been shown to vary greatly in activity. It is hardly worth while to attempt a description and criticism of the many proprietary preparations. It seems more desirable to attempt to review the rules by which the useful preparations can be distinguished from the less valuable. Of course activity as established by a reliable form of biological assay, preferably the cat method of Hatcher and Brody (74) is essential.

The cost and recently the availability, especially of foreign products are to be considered even when the medicinal qualities are satisfactory. As Eggleston (47) has recently stated:

> Of the many proprietary preparations and speciali ties which are offered with high claims for oral administration, none is superior to the powdered leaf or a tincture of high grade, and most are decidedly inferior. All are quite costly and the price of some is exorbitant. If one feels impelled to employ one of these, digipuratum or digipoten will be found to be the best, but these are merely carefully assayed, purified preparations from good digitalis leaves.

The dried aqueous extract recently described by West and Pratt (156) at first seemed to be an excellent preparation but has since proved too hydroscopic. It was used by them in capsules containing 0.1 gram. The chloroform-soluble extract which Hatcher (71) has obtained has been successfully employed by Eggleston (46), and may prove to be superior to the ordinary tincture, on account of its uniformity of absorption.

The infusion of digitalis has no advantage over the tincture or powdered leaves, and the large amount necessary for proper dosage make it less desirable.

Weiss and Hatcher (54a) have recently investigated the relative merits of the infusion and the tincture once more. They found that

the infusion of digitalis prepared according to the method prescribed in the United States Pharmacopoeia does not represent the drug completely, so that its strength cannot be determined from that of the leaf from which it was made. They give a method by which all water-soluble active principles can be obtained. They show that the full strength of the drug is represented by the tincture, and neither the infusion nor the tincture contain amounts of the saponin bodies sufficient to cause undesired effects. Weiss and Hatcher point out that they can find no evidence of any qualitative difference between the actions of the tincture and those of the infusion. The common belief that the infusion deteriorates rapidly is apparently much exaggerated, because Weiss and Hatcher report that an infusion prepared by the method they recommend, kept in hermetically sealed bottles for two years and five months retained its activity unimpaired, as shown by tests on cats and by its therapeutic results. A properly prepared and preserved infusion would seem therefore to have a usefulness quite similar to that of a good high grade tincture.

None of the preparations claiming to be devoid of effects on the gastro-intestinal tract should be used on that account. The absence of this effect must be viewed as evidence of inactivity, because of lack of potency or poor absorption, and if gastric symptoms are not produced, the desirable effects can not be expected.

Strophanthus and squills as well as most of the purer derivatives of digitalis are so poorly and irregularly absorbed from the gastro-intestinal tract that they should never be used for oral administration. Crystalline g-strophanthin is the most satisfactory drug for intravenous use provided it is protected against deterioration by regulation of its reaction and by its being marketed in hard glass containers. The importance of this has been shown by Levy and Cullen (95).

The French preparations, Arnaud's ouabain and Nativelle's crystallized digitaline have been assayed by Levine (93), using the cat method, and he found that this ouabain had a cat unit of 0.059 mgm. It is nearly twice as active as the ouabain used in America, which Hatcher has shown to have a constant unit of 0.1 mgm. Nativelle's crystalline digitalin in sterile oil capsules had a cat unit of 0.86 mgm., the tablets of 0.71 mgm. Levine suggests that the dose of 0.25 mgm. of digitalin advised by the manufacturers is too small

for good therapeutic effects. Perhaps the sterile oil preparation is the most satisfactory for intramuscular injection if such use of the drug be found necessary. It was stated, when the so called digitalis group of drugs was discussed as a whole, that this review would deal almost exclusively with digitalis and strophanthus. Recently three other members of the group, squill, apocynum and convallaria have been investigated from the point of view of their therapeutic effects by White and his collaborators. As their therapeutic value has been compared with that of digitalis, a brief statement may be made regarding their use in the treatment of heart disease. The digitalis-like action of squill was studied in fourteen patients by White, Balboni and Viko (158). Thirteen of their cases showed auricular fibrillation, most of which had been previously shown to respond well to digitalis. They found that ventricular slowing and the characteristic changes in electrocardiograms were produced by the drug, indicating that squill does have a definite digitalis-like action, but only when doses much larger than those usually recommended were given. They administered the tincture of squill, and found that from 8 to 16 cc. were necessary at each dose instead of the recommended dose of 1 cc. (15 minims). No definite diuretic effect could be attributed to the action of the drug. Eggleston, as previously mentioned, stated in discussing this paper that in his opinion the large doses were necessary on account of the poor absorption of the drug from the gastro-intestinal tract. He further says that he can see no reason for using squill in place of digitalis in the treatment of heart disease.

Apocynum and convallaria have been similarly studied by Marvin and White (110a). Apocynum was administered by mouth in the form of the fluid extract to twelve patients. Although the drug was found to have an action similar to digitalis when given to patients with auricular fibrillation, it produced pronounced gastro-intestinal symptoms, which occurred with the smallest doses that had any demonstrable effect on the heart. Its persistence of action was transient, lasting only twenty-four to forty-eight hours. The drug was much less effective in doses that could be given than digitalis in the treatment of heart disease. Convallaria was also given to twelve patients in the form of the fluid extract. It was found to be distinctly less efficacious than digitalis, causing clinical improvement in only two of

the twelve cases. Nausea and vomiting occurred in nine and diarrhoea in six cases. Its action was transient. Marvin and White conclude that

it would seem from our results that neither apocynum nor convallaria can be substituted for digitalis. In our experience digitalis has been characterized by quicker action, more pronounced effects, less discomfort, and more prolonged improvement, than are seen following either of the other drugs. We are convinced that both these members of the digitalis series have no place in the rational treatment of heart failure.

In spite of the fact that these studies bring out, apocynum and convallaria are used to a considerable extent, as two American pharmaceutical companies reported to Marvin that their annual sales amounted to about 15,000 pints.

In the therapeutic use of digitalis certain requirements should be insisted upon by the medical profession. All products put upon the market should be labelled not only with the results of the biological assay, but also with the date of manufacture and of the assay. The dose should be indicated according to the actual strength of that particular preparation. When the medical profession learns to regulate the dosage of the digitalis bodies properly, and to understand thoroughly the indications for their use, the great value of this group of drugs in the treatment of heart-failure will be more generally appreciated even than it is at present. The selection of the form in which the drug is used is relatively unimportant if activity and especially dosage are properly controlled, and if the use of the unsuitable members of the digitalis group is avoided.

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THE TREATMENT OF MENINGOCOCCUS MENINGITIS

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HISTORICAL RÉSUMÉ OF MENINGOCOCCUS MENINGITIS

First appearance

In the early part of the nineteenth century there appeared a form of epidemic disease which had not been observed before or at least it had not been recognized by the physicians of that time. According to Hirsch, it is not clear from the reports in the literature whether the disease previously had really existed. There is no reason to doubt that it had, but if so, it had been confused with many of the other forms of epidemic disease. This new entity was characterized by an inflammation chiefly or entirely localized in the cerebral and spinal meninges and it was accompanied by the symptoms of an acute epidemic constitutional malady.

The disease was first accurately described by Vieusseux, who observed a small epidemic at Geneva in 1805. Small outbreaks followed among the soldiers in the garrisons at Paris (1814), at Metz and Geneva (1815) and at Westphalia (1822). In the United States, cases were reported as far west as Kentucky and Ohio in 1808, and there was a widespread epidemic most prevalent in New England from 1814 to 1816.

The disease was first spoken of as "meningitis cerebrospinalis epidemica" or "typhus cerebralis." In this country it was known as "sinking typhus" or "spotted fever." From the date of its first appearance, meningococcus meningitis, epidemic meningitis or cerebrospinal fever has been epidemic in various places from time to time. These epidemics are followed by quiescent periods in which isolated cases appear and these quiescent periods are in turn followed after greater or less intervals of time by fresh outbreaks. This onward march has continued throughout the last century and up to the present day, so that either in sporadic or epidemic form meningo-

coccus meningitis may justly be spoken of as an endemic disease. When once implanted in a new community, it there remains just as is the case with measles, scarlet fever and other similar diseases so that at present it still prevails in those countries in which it first appeared a century ago.

For many years meningococcus meningitis was regarded as a disease which followed none of the laws which govern the progress of other epidemic diseases. An epidemic would begin as a perfectly isolated incident in a locality that had been altogether free before, run its course there, and then spring up in some quite distant region. The cause of such transmission by means of "carriers" was of course not then known. While the disease is most commonly seen in children, with bad sanitary and overcrowded housing conditions it quickly develops epidemic proportions and affects people of all classes and of all ages. The statistics compiled by Compton show that the most susceptible age for the sporadic form is under five years and the least susceptible from thirty-five to forty years; during epidemics persons of all ages are attacked. Even in epidemics and in the outbreaks occurring in army barracks during the world war, the disease has a seasonal prevalence. The majority of the epidemics have begun in the winter months, the maximum intensity of the epidemic being reached during the spring months and from then on the incidence of disease falls steadily and the epidemic is usually over by the early summer months. Our present conception of meningococcus meningitis is that of an infectious disease, occurring sporadically or in epidemics, due to the diplococcus intracellularis meningitidis, discovered by Weichselbaum. The disease affects children and young adults most frequently, the latter especially when closely confined in army barracks and institutions. It prevails chiefly in the winter and spring months. The mode of infection is by direct contact either with a patient suffering from the disease or contact with a healthy person harboring the organism, a so-called carrier.

Mortality before serum treatment

From a review of the literature it is apparent that the severity of the disease unmodified by treatment has not changed materially since its first recognition. In the earlier epidemics the mortality is

given from 20 to 75 per cent by Hirsch, who collected the statistics from 41 epidemics. The figures before the days of serum treatment, compiled by Flexner, show that the death rate in 18 epidemics was between 42.5 and 90 per cent. In one epidemic the mortality was 42.5 per cent; in three, 60 per cent; in nine, 70 per cent; in two, 80 per cent, and in one, 90 per cent. Statistics show, moreover, that the mortality varies considerably with different epidemics and at different periods of the same epidemic. Fulminating and rapidly fatal cases are by far more frequent at the beginning of epidemics and mild and abortive cases much more frequent toward the close. Sporadic cases are usually mild and the mortality with this form of disease is relatively low.

Treatment before discovery of antimeningococcus serum

As with other diseases whose etiology and pathology have not been clearly understood and in which the views regarding the nature of the disease have changed from time to time, so with meningococcus meningitis the methods of treatment have been ever changing and many diametrically opposed therapeutic measures have been adopted from time to time. Among the most prominent and characteristically different methods have been: a stimulating and tonic method pursued because the disease was one of "utter prostration;" vigorous antiphlogistic measures such as the use of mercury in large quantities or of repeated bleeding, and sedative measures such as the use of large doses of opium.

Emetics were held to be useful if not indispensable in the early stage of the disease and Vieusseux in the first epidemic said "The first principle and often the only remedy was tartar emetic." A half grain was given every ten minutes to produce full and free vomiting and the dose was repeated five or six times or more often according to its effect. "Sometimes it arrested the vomiting, the fever and the pain in the head immediately, and was generally sufficient for the cure." Some writers were less sanguine as to the beneficial effects of emetics and a few indeed condemned their use. Nearly all writers advised them during the early period of the disease with the idea in mind "to scatter the congestion which produced the exudative inflammation of the cerebrospinal membrane, and to aid in eliminating the morbid material of the disease."

In the early epidemics, with the exception of mercury which was not then regarded as a purgative, it was the general consensus of opinion that there was no room for cathartics in this disease. They were even regarded as harmful to the patient. One writer says "The constipation, if any exists, yields usually without purgative medicine; constipation is in fact and as far as it goes a sign of health rather than of disease."

In such an extremely fatal disease and one in which but little hope was held of its arrest by natural means, active measures were used frequently and boldly. Venesection was employed by all. Large quantities of blood were taken from the arm or jugular vein at one time or several bleedings were made in quick succession. As much as 48 and 44½ ounces of blood have been removed from an adult on separate occasions. In a child, 48 ounces of blood were taken by cups from the neck and occiput and 26 ounces from a vein in the arm within eighteen hours. Local blood-letting did seem to be followed by some good results, especially in the sthenic cases. The effects were not regarded as satisfactory although in many cases there was noted an improvement in the pulse rate and relief from the excruciating pain in the head. But the general impression prevailed that while blood-letting afforded considerable relief to the patient in the early stages, it was a disappointment from a curative point of view.

Cold to the head and spine, leaches to the head, blisters and dry and wet cupping were used for the relief of the severe pain and afforded some relief and comfort to the sufferers. Great stress was laid upon the necessity for maintaining the bodily heat and for keeping the skin moist. Warm and hot baths, bottles of hot water, billets of wood heated in boiling water and wrapped in flannels, hot infusions, etc., were considered of great help in combating the violent symptoms as well as the symptoms of collapse.

Alcohol, opium, iodide of potassium and other drugs were used generously and their usefulness and indications were the subject of much discussion. There were many who believed that alcoholic stimulants were absolutely necessary "to support the vital energy, to raise the patient from his depressed state and to hold him up until the disease passes off." Other writers, especially the European writers, were more skeptical of the use of stimulants and condemned

their liberal and indiscriminate administration. Opium enjoyed the reputation of being a specific for meningococcus meningitis. It was given by some in small doses and by others in large doses; although its curative effects were grossly overestimated, it was observed that "the pain and spasm subsided, the skin became warmer, the pulse fuller and the entire condition of the patient became more hopeful" after its administration. Iodide of potassium was extensively employed to promote absorption during the late stage of the disease.

Among the active measures advised in the treatment in the early epidemics, mercury perhaps was used more generally than any other medicine. Mercury was given by mouth or inunction even to the point of salivation, but as with the other measures adopted, we find a diversity of opinion regarding its beneficial effects. Other measures such as the proper use of a nutritious diet and of tonic medicines received their share of attention.

Stillé concisely stated the opinions regarding the peculiarities of the disease and its treatment which were held during the early history of the disease. He said:

> In epidemic meningitis as in other acute and especially epidemic diseases, many cases are fatal from the outset; the first symptoms of the attack are the first phenomena of death; on the other hand many are so slight as scarcely to require medicinal interference for their cure. But the event of many others is determined by the appropriateness and the opportuneness of the treatment . . . . but their successful application depends upon the sagacity of the physician.

The use of the more modern measures, repeated lumbar puncture, the intraspinous injection of antiseptics, permanent drainage, etc., in the treatment of meningococcus meningitis will be discussed later.

THE MENINGOCOCCUS AND ITS STRAINS

The micrococcus intracellularis meningitidis was first accurately described by Weichselbaum in 1887 as a Gram-negative coccus, usually occurring in pairs. Prior to, as well as subsequent to his report, it had erroneously been stated that this organism was Gram-positive. The meningococcus, except for older laboratory strains

which can thrive on plain agar, grows only on media enriched with blood, ascitic fluid or starch. The colonies are round, perfectly lenticular with smooth edges, are translucent by transmitted light and a bluish gray by reflected light. They are rarely over 2 mm. in diameter. The optimum temperature for growth is 37.5°C.; comparatively slight variations from this will retard the growth on culture media. The meningococcus is sensitive to drying and cultures rarely survive longer than seven days. Recently it has been demonstrated that reduced oxygen tension greatly facilitates cultivation of the meningococcus.

Like the gonococcus, the meningococcus ferments dextrose and maltose. For a time it was difficult to differentiate these two organisms except by noting their origin. They are, however, distinct as was rather drastically proven by injecting cultures of each into the urethra of two healthy men. The individual receiving the gonococcus developed gonorrhea while the one receiving the meningococcus had no reaction. These two organisms are frequently agglutinated by the same sera, but Ellis in 1915 demonstrated that the immediate agglutination reactions are specific, i.e., that even at dilutions of 1:2, meningococcus sera would only agglutinate the meningococcus immediately or within one-half hour while after an interval of an hour or so the gonococcus would also be agglutinated.

In 1909, Dopter isolated an organism from the spinal fluid of a patient with meningitis that had all of the morphological and cultural characteristics of the meningococcus but was not agglutinated by the usual meningococcus serum. This organism he called the parameningococcus. Wollstein not only corroborated Dopter's observation but found that there were a number of intermediate strains which although similar could be distinguished serologically from the normal and the parameningococcus. Later, still further variants were reported. Gordon immunized a series of rabbits with 34 cultures of meningococci collected during the early part of the war and carried out agglutination and absorption reactions with his strains. He found that they fell into four groups which he designated as I, II, III and IV. I and III, and II and IV were closely related, and their sera showed cross agglutination but they could be separated by absorption tests. Groups I and II were the more common. Ellis

by more or less similar methods described three groups. Nicolle and his co-workers at the Pasteur Institute reported four divisions of meningococci, namely, A, B, C and D, of which B was identical with Dopter's parameningococcus. At the Rockefeller Institute two main groups of meningococci, the normal and paranormal and two or more intermediates are recognized. Many attempts have been made to classify the groups described by these various authors. In Davison's experience, the Pasteur A, Gordon's I and III and the Rockefeller Institute paranormal are agglutinated by the same sera and the Pasteur B, Gordon's II and IV and the Rockefeller Institute normal by the same sera. These two main divisions of four groups each are those most frequently encountered. It is interesting that in England in 1914 and 1915 the members of the first group were the more common, not only in the army but also among the civilian population while during 1917 and 1918 the members of the second group were the more frequent, possibly indicating that an immunity had arisen against the members of the first group. The Pasteur C and D, Gordon's III and IV and the Rockefeller Institute intermediates are comparatively rare.

THE DISCOVERY OF A SPECIFIC SERUM

The discovery of the meningococcus and the gradual development of the routine employment of lumbar puncture resulted in a clearer understanding of meningococcus meningitis and made it possible to establish an accurate diagnosis, which before had been impossible. In spite of these important observations, no therapeutic measures were suggested which in any way influenced the heavy mortality until the discovery of antimeningococcus serum. The production of the specific serum is the direct result of the world wide epidemic which continued almost without cessation from 1904 to 1910. Almost simultaneously Jochmann in Germany and Flexner in New York studied the production of specific immune sera which would protect small animals against infection with meningococci. They could protect small animals and Flexner was able to cure meningitis, artificially produced in the monkey by the intraspinous injection of an immune serum which he prepared. Antimeningococcus serum for use in human beings was produced on a large scale by the immunization of the horse.

In 1906, Jochmann reported the results with 11 cases of meningitis in human beings treated by the intraspinous injection of serum, and in 1907, Kolle and Wassermann who also had prepared an immune serum reported the results of treatment in 57 cases of meningococcus meningitis. In 1908, Flexner and Jobling published a comprehensive report of serum treated cases. There was an appreciable alteration in the death rate in all cases treated when the injection was made into the subarachnoid space. Park in 1905 had used an antimenigococcus serum which he had prepared in the treatment of 20 cases by subcutaneous injection. The results were not satisfactory. The serum was at first injected subcutaneously and intravenously as well as intraspinously, but later the intraspinous method alone was employed by all. Thus, as the direct result of scientific research, a satisfactory specific serum therapy was finally developed. For more than fifteen years antimeningococcus serum has now been used and its efficacy is universally admitted.

THE PREPARATION OF ANTIMENINGOCOCCUS SERUM

The production of antimeningococcus serum was first accomplished by Jochmann by injecting cultures of the meningococcus heated to 60°C. for one-half hour intravenously into horses. Increasing doses of killed organisms were injected at stated intervals and later the horses were injected with cultures of living meningococci. Kolle and Wassermann in addition to the killed and living organisms injected the autolysate as well, as they thought the soluble products of the meningococcus increased the potency of the serum. Flexner, who used at first increasing doses of killed organisms, then increasing amounts of autolysate and then living cultures by the combined subcutaneous and intravenous method, finally discarded the intravenous method as the injections were followed by such severe and alarming reactions and resorted to the subcutaneous injection of cultures and autolysate alternately at seven-day intervals. Subcutaneous inoculations were followed by a mild febrile reaction during which the animal ate less but did not suffer from other symptoms. The dose was gradually increased from 1 to 2 and 3, etc., loops of cultures to the amount contained in one and a half small culture bottles and the dose of autolysate was increased to the equivalent of one and

one-half bottles of the cultures. Many different strains of meningococci were employed in the production of Flexner's serum. As new strains were found, they were added to those already in use in order to have antibodies in the serum which corresponded to all the recognized strains. Immunization in the horse is a slow process and sera withdrawn less than six months after the beginning of injections are apt to be deficient in antibodies. The antiserum first used by Flexner was obtained from a horse who had been in process of immunization over one year. After the discovery of the two main types of meningococci, the normal and parameningococcus, representatives of these two types were used in the preparation of sera either in mixtures or with alternate injections of the two types. It was learned that the employment of representative normal and representative parameningococcus strains was not sufficient for immunization as within each group there were organisms which reacted weakly to the specific antibodies produced by other strains of the same group. When the weakly reacting strains were inoculated, antibodies were formed to which they reacted strongly. So not only one but several strains of each group were employed for the purpose of immunization of the horses. It is of the utmost importance that serum used therapeutically contains the antibodies specific for the infecting strain.

Rapid method of preparing serum

As mentioned before, from six to twelve months were required to produce a meningococcus serum of high potency by the old method of immunization. The increase in the number of cases of meningococcus meningitis which was evident in the early days of the great war made it imperative that a larger amount of serum would be necessary than could be supplied by the ordinary methods of production. For this reason and because much of the sera prepared by the commercial houses had given such irregular and disappointing results, the preparation of serum in large quantities was undertaken at the Rockefeller Institute. Amoss and Wollstein have produced a polyvalent serum of high titre. By first desensitizing the horse before employing the full inoculation of the culture, according to the technique of Briot and Dopter, the severe reactions usually occur-

ring after intravenous injection were avoided. Three successive cultures of representative strains of meningococci and their autolysate were injected intravenously at regular intervals. Specific immune bodies appear early in this serum and increase rapidly. A potent serum was produced in eight or twelve weeks instead of the eight or twelve months which the older method required. This serum has been successfully employed in the treatment of meningococcus meningitis.

Many sera of high potency are prepared and can be obtained. The most satisfactory, however, have been those prepared by research laboratories: the Rockefeller Institute in this country and the Pasteur Institute in France. The Lister Institute now prepares a polyvalent serum in which the horses are immunized by the four representative strains of meningococci differentiated by Gordon. The experience of the British forces with commercially prepared antimeningococcus sera should not be forgotten for it emphasizes the necessity for the standardization of sera prepared by commercial laboratories. Sera should not only contain antibodies for the four representative strains of meningococci and be of high titre but they should not be colored by hemoglobin compounds and a harmless chemical preservative should be used. Tricresol not only will prevent contamination of serum which has been collected and bottled in a sterile manner but it has an analgesic effect also.

Standardization of serum

Different opinions are held regarding the methods for determining the therapeutic value of antimeningococcus serum, as it is much more difficult to determine the potency of an antibacterial serum than of an antitoxic serum, such, for instance, as diphtheria antitoxin. Krauss and Dörr believe that the chief action of the serum depends upon its antitoxic properties; Jochmann, Flexner and Wassermann believe that the chief action of antimeningococcus sera is to increase phagocytosis of the microörganism, to destroy the meningococcus and to neutralize toxins. It has been shown that antimeningococcus serum probably contains bacteriolysins, opsonins, antiendotoxins, agglutinins, precipitins and complement fixation bodies. The presence of many of these does not necessarily have any influence on

the therapeutic activity of the serum. Different writers have suggested the use of various tests to fix a proper standard for antimeningococcus serum but the difficulty in using any one criterion as a standard for measuring the several forms of activity is apparent. The opsonin and the complement fixation methods have practically been discarded as it is not possible to determine by them the antibodies representing the different types of meningococci. The antiendotoxic standard as applied by Dopter, Wassermann, Krause, Leuchs and others has been criticized by Gordon on the ground that the content of endotoxin was too low to be used for purposes of standardization. Before this method becomes an acceptable method of standardizing meningococcus serum, the presence of a meningococcic endotoxin must definitely be proven. The workers in the Hygienic Laboratory in Washington have failed so far to confirm the presence of an anti-endotoxin in the sera which they have tested (Leak). The protective power of antimeningococcus serum for small animals has been used as a method of standardization. The test is made by mixing varying amounts of a meningococcus emulsion with a definite quantity of immune serum and injecting this mixture into the peritoneal cavity of animals. Hitchens and Robinson have described a protection test with mice and believe that the animal protection test is more nearly indicative of the potency of the serum than is the agglutination test or the complement fixation test. They also suggest that the amount of serum necessary to protect against one minimum lethal dose of culture be used as a uniform standard for antimeningococcus sera. Amoss and March were unable to confirm their results and regard the protective power of antimeningococcus serum for laboratory animals as a variable and unsuitable index of its value.

At the present time the determination of the agglutinin content of sera is considered, in this country, the most reliable method for the standardization of antimeningococcus sera. Although the part played by agglutinins in overcoming infection is not known, it has been demonstrated that a high agglutination titre is usually accompanied by a strong complement binding power and a high opsonic index. It is therefore reasonable to suppose that a serum possessing these properties has a relatively high antibody content. Practical experience has shown that sera showing a high agglutination titre for the

meningococci isolated from patients' cerebrospinal fluid as a rule give good therapeutic results. On the other hand, as the French writers have pointed out, satisfactory clinical results may at times be secured by the use of sera with a low agglutination power. At present it must be admitted that the methods of determining the potency of antimeningitis sera leave much to be desired. The New York State Board of Health requires that serum should be prepared from four properly chosen cultures of meningococci and a standard value based on the agglutination titre. Serum used in treatment of this disease should contain antibodies for the two main types of organisms and the subtypes.

Serum for diagnostic purposes

Polyvalent and monovalent antimeningococcus sera are used, in the laboratory, for identifying the meningococcus, for determining the various types of meningococci and for testing the potency of different sera. The therapeutic polyvalent serum prepared in the horse is used for this purpose. Monovalent sera are made in young rabbits according to two methods. Amoss prepares his serum by suspending a sixteen-hour growth of the meningococcus in 10 cc. of 0.8 per cent salt solution. Of the suspension 0.1 cc. is diluted to 2 cc. and injected intravenously. The same dose with a fresh culture is repeated on the second day and one-eightieth of a culture on the third day. After five days, one-eightieth of a culture, then one-fiftieth and finally one-twenty-fifth on the third day are injected. Two days later the rabbit is sacrificed and the serum collected. Hines prepares his serum by injecting increasing doses of an emulsion of meningococci killed by heat. The serum is preserved with phenol. By either one of these methods satisfactory sera for identification of the type of meningococcus by the agglutination test are prepared. The reader is referred to text books for a description of these tests.

DIAGNOSIS OF MENINGOCOCCUS MENINGITIS

In the early stage of meningococcus infections before the localization of the organism in the meninges with the resulting symptoms of meningeal irritation, diagnosis is well nigh impossible except in the presence of an epidemic. Even with the aid of blood cultures diag-

nosis before the onset of meningitis is most difficult. The symptoms at the onset may be so mild and so insidious that several days may elapse before the true nature of the infection is recognized, or it may be so severe and fulminating that the patient dies within the first twelve to thirty-six hours. A sudden onset with chills, marked prostration and headache, together with vomiting, is highly suggestive of meningococcus meningitis, especially when there is a petechial or purpuric rash. The characteristic but by no means pathognomonic eruption occurs at some time or other during the course of the disease in about 50 per cent of the cases. As it is not a constant finding, it cannot always be relied upon. Occasionally one sees patients within the first few hours of the onset without meningeal symptoms when petechiae are present but in the majority of cases meningococci will be found in the cerebrospinal fluid if it is examined even at such an early period. Although a tentative diagnosis of meningococcus meningitis may be made when a patient who previously has been well has an acute onset with headache, vomiting, a chill or convulsions and who presents the signs of meningeal irritation (cervical rigidity, hyperaesthesia, Kernig's sign, Macewen's sign or a tense and bulging fontanelle), the final diagnosis always rests on the actual demonstration of meningococci in the cerebrospinal fluid. A differentiation between meningitis due to the pneumococcus, streptococcus, staphylococcus aureus and other organisms and between other diseases, pneumonia, typhoid fever, typhus fever, cerebral abscess, simulating meningococcus meningitis, can be made in no other way than by lumbar puncture and the demonstration of the organism. A clinical diagnosis without bacteriological proof is always open to criticism. In the very early stages the cerebrospinal fluid may appear clear yet the meningococcus can often be demonstrated in both stained smears and cultures. As the disease progresses the cerebrospinal fluid becomes turbid and intracellular and extracellular Gram-negative diplococci can usually be made out readily. In almost all cases they will be found after prolonged search. In the subacute and chronic cases the demonstration of the meningococcus may be attended with great difficulty. I have seen patients in whom it was impossible to demonstrate the organism either by smear or by culture in the cerebrospinal fluid at the first puncture but in subsequent punctures

they appeared in large numbers. In some patients, particularly children, when the disease has been present for some days, there may be an obstruction to free communication between the spinal subarachnoid space and the interior of the ventricles. In these circumstances it sometimes happens that no fluid can be obtained by lumbar puncture or the fluid that is obtained may be free from meningococci whereas the ventricular fluid contains the organisms in large number. Only by means of a ventricular puncture is it possible to obtain cerebrospinal fluid and so demonstrate meningococci. This may readily be accomplished in children with an open fontanelle which is the age at which the severance of the communication is more likely to occur. Relatively few cases are seen in which meningococci cannot be demonstrated by persistent search in the cerebrospinal fluid removed from the ventricle or lumbar subarachnoid space at different times. That such cases do occur and recover after specific therapy should be borne in mind. In a series of 202 cases of meningococcus meningitis which I have seen during the past few years, there were 13 cases in which meningococci were not demonstrated in smear or by cultivation. Corroborative evidence of the existence of meningococcus infection may be had by demonstrating the organism in the rhino-pharynx of such patients. The following case is cited as an example:

J. D., white, age seven years. Patient was admitted to the Harriet Lane Home on the 114th day of the disease, with a history of recurrent attacks of fever, headache, vomiting, drowsiness, muscular rigidity and opisthotonus. On admission, examination revealed nothing abnormal except emaciation, hyperactive reflexes and slight engorgement of the vessels of the fundi.

Temperature, 99.6°F, white blood cells, 16,700. Pirquet negative. Wassermann negative. Urine normal. Blood culture sterile. Throat culture showed meningococci.

Spinal fluid: No increase of pressure, slightly cloudy, 2800 white blood cells; 76 per cent polymorphonuclears. Pandy strongly positive, Wassermann negative. No organisms found in smears. Culture sterile.

Treatment: Six lumbar punctures were done and antimeningococcus serum injected three times. The spinal fluid gradually became clear, cell count fell to 32 per cubic millimeter. Pandy test remained positive. Repeated

examinations failed to show organisms in smears and repeated cultures were sterile. The patient was apparently well 122 days after the onset of the disease.

PROPHYLACTIC MEASURES IN MENINGITIS

Epidemiological studies of meningococcus meningitis have established without doubt that the disease is spread by direct contact from one person to another, as is the case with diphtheria, poliomyelitis, etc. More than twenty years ago Councilman, Mallory and Wright, Kiefer and others demonstrated that the meningococcus is present in the rhino-pharynx of patients suffering from meningococcus meningitis. In 1901, Albrecht and Ghon demonstrated its presence in healthy persons. Since then it has been generally accepted that the disease is spread by means of the rhino-pharyngeal secretions that harbor the meningococci. Therefore, from the standpoint of the management of meningococcus meningitis, prophylaxis may be said to equal in importance specific serum treatment. As ill persons are usually confined to their beds, they are of menace only to physicians, to attendants and to other patients and do not become a menace to others until the convalescent stage.

Meningococcus carriers

The healthy carrier is the greater menace to the community. The disease is spread by those who have suffered from the disease, and by those who have never been ill. The meningococcus may remain in the rhino-pharynx of a carrier for a variable length of time and for that reason two classes of carriers can be distinguished, the acute or transient carrier and the prolonged or chronic carrier. Attendants and relatives constitute the larger percentage of the acute carriers, and usually the meningococcus remains in the rhino-pharynx for only a short period of time. It may be found at one examination and not at subsequent ones. The British Medical Research Committee found that of 119 people who had been in contact with meningitis patients, themselves not being ill, 94 harbored organisms of the same type as had caused disease in the patient with whom they had been in contact. The chronic carrier is different. He has usually suffered from the disease himself and the organism persists for months, even

years, and while it occasionally disappears, it subsequently reappears. The spread of the meningococcus, an organism which does not withstand, easily, exposure to air, is accounted for by chronic carriers. These are in all probability responsible for the spread of the disease from place to place and for the causation of epidemics. If it were not for them the disease might readily die out. The cycle of events which leads to contamination and to infection has been summarized by Flexner as follows: "A meningococcus carrier is introduced into a group of persons of the more susceptible ages. Of the latter a certain number become contaminated through aspirating the rhino-pharyngeal secretions which he ejects. Of those thus contaminated a variable number actually become infected and develop meningitis while a larger number are converted either into temporary (evanescent) or more enduring (chronic) carriers. The patient during the acute illness and for an indefinite period while convalescent is also a carrier. Hence the number of carriers produced exceeds the number of cases of infection, from which it may be concluded that the individual susceptibility to epidemic meningitis is low." It has been shown by a number of workers (Mayer) that the percentage of healthy carriers both in the civil population and in garrisons is generally about 3 per cent. The constant occurrence of sporadic cases of meningococcus meningitis is thus readily explained. There must be subsidiary factors, however, to explain the occurrence of local and general epidemics. It is difficult to account for the sudden occurrence of a widespread epidemic of meningitis in a city in which meningitis has been endemic for years. An alteration of the type and virulence of the bacterium or the introduction of a new type of increased virulence suggest themselves as explanations but they are explanations without proof.

Hygienic measures

The regulation of the factors that produce local epidemics constitute the more important hygienic measures which should be observed in the management of patients with meningococcus meningitis. These factors are chiefly overcrowding and poor ventilation. Proper ventilation must be maintained at all costs and the prevention of overcrowding is imperative. By these measures especially in insti-

tutions, in barracks and on ships the risk of the contamination of persons by contact with carriers is greatly lessened. The rise in the incidence of the disease during the cold and damp months of the year undoubtedly is to be explained by the tendency of individuals to congregate together in poorly ventilated and overheated rooms. In a British naval barrack during the month of October, there were 23 cases of cerebrospinal fever, the number of cases immediately fell to 6 for November and 2 for December with the order that the windows should be open day and night and the hammocks hung not closer than every $2\frac{1}{2}$ feet (Rolleston). Free ventilation, isolation and a proper amount of space are as necessary for the treatment of patients with meningococcus meningitis as for the prevention of the disease. Attention should be given to the prevention of overfatigue and the control of rhino-pharyngeal infections—factors which have a tendency to favor the spread of the disease. The proper observing of these principles is of particular importance during time of war and in epidemic areas where there are large numbers of individuals crowded together in barracks improperly ventilated. It was shown by Mayer and his colleagues that there were 2.46 per cent carriers among 1911 soldiers in barracks during epidemic free times whilst the Medical Research Committee found 8.53 per cent among 1629 soldiers who had been in contact with 60 cases of meningococcus meningitis.

The prevention of infection of attendants in charge of patients with meningococcus meningitis is chiefly concerned with the discharges from the rhino-pharynx. It is advisable that patients be isolated either in separate cubicles or by the less expensive method of separating the beds by intervals of $2\frac{1}{2}$ feet and hanging sheets between them. The attendants should not expose themselves to the breath of the patients; they should be protected by wearing caps, gowns and mouthpieces when caring for patients. Nurses should thoroughly cleanse their hands with soap and water and a disinfectant solution after each contact with patients and with all articles used by patients. The discharges from the nose and throat, the conjunctivae, and herpes, and excreta should be destroyed. All articles which come in contact with patients should be kept separate and thoroughly disinfected. Cerebrospinal fluid and the apparatus used in giving treatments should receive special care and sterilization. Cultures should

be taken at stated intervals from those in attendance on patients to be sure that they have not become carriers. Convalescent patients should not be discharged from quarantine until it has been proved that meningococci are not present in the rhino-pharynx.

Prevention of the spread of meningococcus meningitis depends on the detection of carriers, their isolation and their treatment. The question of general examinations for the detection of carriers of the meningococcus has received much attenton especially during the epidemic which occurred among troops during the late war. Certain investigators (Flexner, Parkes, etc.) believe that the incidence of the disease was lower among the troops in which routine search for carriers had been carried out, whilst others, notably Galambos Klinger, Rouman, etc., believe that the incidence of the disease is not influenced by the detection and segregation of the healthy carriers. The bacteriological control of carriers with their detention and proper treatment is the only means of properly checking and preventing the spread of the disease. Indeed, the disease might be exterminated if it were possible to detect and isolate all the carriers of the meningococcus. The difficulties, however, are too great at the present time to carry out such drastic measures as this would entail. The search for carriers among contacts should, however, be carried out whenever meningococcus meningitis arises and the carriers should be isolated and proper treatment instituted. The carriers should be kept isolated until three successive negative cultures at five-day intervals have been obtained. A regulated period of quarantine is quite useless and effective control can only be had by bacteriological proof of negative cultures. The bacteriological detection of carriers necessitates careful technique in the making of the cultures and the cultivation of the meningococcus, the identification and differentiation from other Gram-negative cocci, which frequent the rhino-pharynx, agglutination tests and the recognition of the different types.[1]

The transient carrier usually becomes free from meningococci in a week or ten days and the number of colonies grown from the rhino-

[1] The reader is referred to the standard technique of meningococcus carrier detection adopted by the Medical Department of the United States Army and Navy and the United States Public Health Service for detailed information regarding the methods in use.

pharynx is much fewer than is the case with the chronic carrier. Carriers should be separated from those who have become negative in order to prevent reinfection and carriers should be separated according to the type of organism to prevent cross infection. The chronic carrier is the greatest menace to the community and offers the greatest problem in treatment. As Flack has shown, the persistence of the carrier state varies within fairly wide limits. Among 185 carriers, 124 were known to have been in contact with a case of meningitis or another carrier, whereas 61 had not been in contact either with a patient or with a carrier. The average duration among the former was 4.65 and among the latter 3.68 weeks. Twenty per cent of the 185 carriers became free of organisms within the first two weeks, 52 per cent within the first four weeks and 5 per cent persisted beyond twelve weeks. It was noticed that sunshine and dry weather apparently influenced the rapidity with which the carriers became free. In February and March, the rate of discharge of carriers from isolation was slow whilst with the coming of sunshine and dry weather in April the rate of discharge was increased. Although in the great majority of carriers the rhino-pharynx is normal, the meningococcus persists for a longer time in those who are subject to inflammatory conditions of the rhino-pharynx and accessory sinuses.

Treatment of carriers

It is clear that the meningococcus disappears from the rhino-pharynx spontaneously in the overwhelming majority of carriers. Fresh, dry air and sunshine undoubtedly have an important and favorable influence on the rapidity with which the meningococci disappear. Chronic inflammatory conditions of the rhino-pharynx require appropriate treatment. Aside from these measures the efforts to hasten the disappearance of the meningococci in convalescent patients and carriers by antiseptics have been most discouraging. As the meningococcus is one of the least resistant of the pathogenic organisms to disinfectants, it seems surprising that a means of destroying it has not been found. The reason probably is not so much its resistance to the various antiseptics which have been employed as the difficulty in bringing the solution actually in contact with the organism in the

rhino-pharynx and accessory sinuses. Strong antiseptics by injuring the mucous membrane and setting up inflammatory conditions actually prolong the carrier state (Fulloch). Many methods with mild antiseptics have received careful trial. Swabs, douches, sprays and vapors have been employed. Antiseptics which destroy the meningococcus in vitro fail to destroy the organisms when they are used in the human being. Colebrook and Tanner in tests made upon the meningococcus contained in a film of nasal secretion found that weak carbolic acid solutions and a 5 per cent suspension of "argentine" killed the meningococci. The substance was non-irritating to the mucous membrane and temporarily rendered the carrier free from meningococcus; the organism, however, reappeared in the majority of cases. Attempts with zinc sulphate and pyocyanase have also been unsuccessful. Kutscher after the recommendation by Kolle and Wassermann reported satisfactory results with the nasal sprays of dry antimeningococcus serum. Their results were not confirmed by other observers. Many different substances have been tried in the form of vapors and inhalants. Compounds of iodine, guaiacol, thymol and alcohol were tried by Vincent and Vellot. These likewise have not been followed by very satisfactory results. Sophian found that a 0.5 per cent hydrogen peroxide solution used as a nasal spray and gargle rendered the rhino-pharynx free from meningococci in the majority of cases within a few days to two weeks. Normal salt solution and potassium permanganate solution have likewise been tried, but as has been the case with the other methods which have been employed, although the organism tends to disappear, it usually reappears after a few days. Worster-Drought and Kennedy used extensively a solution of chloramine T of 2 per cent strength diluted with warm water just before use. The solution was applied for three days before cultures were taken. If positive cultures were then obtained, a second course of treatment was usually given. They concluded from their results that chloramine T used as a nasal douche is of definite value in the treatment of meningococcus carriers. It should be carried out, however, under personal supervision. Inasmuch as chloramine compounds do not cause albuminous precipitation in secretions, it would seem that they might find a useful place in the treatment of carriers. The value of chloramine T, however, has not

been substantiated by other workers. Inhalation chambers as used by Kuster and automatic spraying apparatuses suggested by Gordon and Flack, in which chloramine T and zinc sulphate were used have given only fairly satisfactory results. Dichloramine T as suggested by Dunham and Dakin dissolved in eucalyptol in 2 per cent solution has also been used. It should be borne in mind that inasmuch as so many different measures cause the meningococcus temporarily to disappear from the rhino-pharynx a sufficient length of time should pass between the cessation of treatment and the taking of swabs before an individual is discharged and regarded as free from meningococci. Although there is some difference of opinion as to the value of these different local antiseptics in the treatment of meningococcus carriers, the majority of authors regard local treatment as a valueless procedure.

The specific treatment of meningococcus carriers has lately received considerable attention. This has been carried out by means of active immunization with vaccines given subcutaneously in doses of from 50,000,000 to 2,000,000,000. The injection of the vaccine used by Colebrook and Tanner gives very slight constitutional disturbances which pass off quickly. In their series five out of the ten carriers became negative and the other five cases were unaffected. The meningococcus later reappeared in the negative cases. It is scarcely to be expected that the immunization of carriers would have any effect upon the meningococci in the rhino-pharynx inasmuch as recently shown by Gates the blood serum of chronic carriers does already contain agglutinins.

Passive immunity as a prophylactic measure

The production of passive immunity by the injection of antimeningococcus serum and of active immunity by treatment with vaccines has been advocated as a prophylactic measure by a number of different workers. The experiments of Jochmann in 1906 when he produced passive immunity in animals by the use of serum suggested to him that this might be a useful measure in the prevention of the disease. With the exception of Ruppel who recommended its use in 1907, the method was not employed extensively until the 1912 epidemic in Texas. Sophian advised its use as a prophylactic measure

among the attendants who came in direct contact with the patients with meningococcus meningitis. He recommended the subcutaneous injection of 10 to 20 cc. of serum. The dosage is necessarily arbitrary and depends on the serum used. The duration of the immunity afforded was considered one month and in Sophian's cases only one of the persons inoculated contracted the disease. He was a porter who developed meningitis six weeks after the preventive treatment. The chief objection to the prophylactic use of antimeningococcus serum is that the passive immunity conferred is only temporary. The occurrence of serum sickness and the danger of anaphylactic shock if subsequent injections of serum are necessary should not be considered as contraindications to its use any more than they are contraindications to the use of diphtheria or tetanus antitoxin provided the antimeningitis serum is an effective prophylactic. That there is doubt of this is shown by the fact that in the epidemics of the world war it was not extensively employed.

Active immunity as a prophylactic measure

Active immunization by means of meningococcus vaccines had not been used extensively before the war. It has been known for a long time that a certain degree of immunity develops during the active stage of meningitis. This has been demonstrated by complement fixation tests, by agglutination tests and by the estimation of the opsonic index. These same tests have shown that the immune bodies increase in laboratory animals after vaccination. Because of these facts and because of the analogy of meningococcus meningitis to other bacterial diseases, Sophian employed vaccination as a prophylactic measure in the epidemic in Texas in 1912. The results were inconclusive as most of the vaccinated persons did not complete the series of injections. Later Sophian and Black studied the agglutination and the complement fixation of the serum of ten students who had been vaccinated with two or three doses of a monovalent vaccine. The doses given were 500,000,000 to 2,000,000,000 organisms at seven-day intervals. Following the vaccinations severe constitutional reactions occurred. They found the agglutinin titers of the sera of their vaccinated subjects to range from 1:200 to 1:1500. Complement was fixed in serum dilutions up to 1:250. Comple-

ment fixing antibodies were found in low dilutions in the serum of seven of these men after an interval of two years. Sophian and Black refer to Hall's experience in Kansas City in the vaccination of about 280 persons in families in which meningitis had occurred. A number of doctors and nurses were likewise vaccinated. In no instance did the disease occur subsequent to vaccination.

During the war preventive vaccine therapy was extensively employed. Greenwood believes from his experience with 4000 men inoculated twice, first with 250,000,000 to 300,000,000 and after a week with 1,000,000,000 bacteria, none of whom contracted the disease, that vaccination is a valuable prophylactic procedure. Gates using a vaccine prepared from the two main types of meningococci vaccinated 2700 soldiers at three-week intervals with 2,000,000,000, 4,000,000,000 or 8,000,000,000 cocci. He found that these doses rarely caused more than a mild reaction except in certain susceptible individuals. In the severe reactions the symptoms simulated the onset of meningitis but they lasted only a few hours. He demonstrated specific agglutinins for meningococci in the blood serum of the vaccinated men. Among the men treated by Gates two patients who had, probably, been vaccinated during the incubation period of the disease developed meningococcus meningitis. Another patient developed meningitis at a time when immunity should have been established. During a period of four months while under observation, no cases of meningitis were known to have occurred among the others who were vaccinated. Chalmers and O'Farrell working in the Soudan report somewhat similar results using much smaller doses. They began with 5,000,000 and never exceeded 100,000,000, Treadgold using 50,000,000 and one week later 100,000,000 organisms vaccinated 79 carriers, none of whom developed meningitis and Aaser gave two doses of 300,000,000 organisms each at five-day intervals to 1200 soldiers. No vaccinated soldiers developed the disease. Recently Whitmore and his colleagues, using a polyvalent lipo-vaccine, inoculated 55 men with 40,000,000,000 and 80,000,000,000 organisms subcutaneously in one or two injections. They reported that the use of such vaccines diminish the risk of reaction. In the first days after vaccination agglutination formation was observed against three of the vaccine strains. Although the evidence thus far collected

would seem to favor prophylactic meningococcus vaccination, further studies need to be carried out, on account of the resistance to the disease which most persons possess, before it can be stated that the measure is as important in preventive medicine as is typhoid vaccination. There are no insurmountable objections to its use.

TREATMENT

Specific serum therapy has established itself by tests under such a variety of conditions and over such a long period of time that the efficacy of this form of treatment in meningococcus infections cannot be questioned. There is however a very considerable mortality, in the neighborhood of 25 per cent, even when patients are treated intelligently and energetically. It is not surprising therefore that efforts have been made still further to improve the methods of treatment.

The premeningitic stage of meningitis

It is becoming more and more evident not alone from clinical observation but as the result of experimental work that the first stage of a meningitis in all probability is usually preceded by a bacteriemia. It is generally but not invariably a transitory invasion, the bacteria disappearing as a rule from the blood stream in a very few days. While the older view, that the infection results from the direct extension of the organism through the cribiform plate of the ethmoid or from the sphenoidal or ethmoidal sinuses to the base of the brain, has not been disproven, the majority of observers are of the opinion that the meningococcus gains access to the blood stream through the upper air passages and then becomes localized in the meninges. The question then arises is it possible to recognize meninococcus infection in the premeningitic stage and if it is possible, is treatment at that stage effective. It is very difficult to answer these questions. Meningococci may be found in the blood in a certain proportion of cases of meningitis. They disappear rapidly shortly after the time of their localization in the meninges. They disappear whether antimeningococcus serum is used or not for it is very difficult, usually impossible, to cultivate them from the blood even in untreated cases after the meningitis has lasted several days. It is very likely, indeed

most probable, that meningococci often find their way into the blood and are there destroyed and never become localized in the meninges. In these circumstances the illness would be passed over as a febrile reaction of undiscoverable origin. If blood cultures were made from such cases, as might be done in the midst of an epidemic in an army or navy, meningococci discovered and some form of therapy instituted, favorable results might be ascribed to this form of therapy which were not merited, in the same way that favorable results might be ascribed to some form of therapy in abortive cases of poliomyelitis. Furthermore there are certain cases of meningococcus sepsis in which meningeal localization never occurs. They run their course, recovery often taking place, uninfluenced by treatment.

Intravenous serum therapy

As a result of many studies during the recent war intravenous serum therapy has been warmly recommended by some authors or believed to be indicated by others. These authors are Herrick, Baeslack, Worster-Drought and Kennedy, Golden, Loch and Hebert, Hayden and others. It is maintained that the serum should be given intravenously in large doses to overwhelm the infection within the first twelve to twenty-four hours before the localization of the organism in the meninges. When meningitis has been established it is recommended that the combination of serum both intravenously and intraspinously with repeated spinal punctures should be carried out. The routine method outlined by Herrick is as follows: On admission a patient presenting the early symptoms of meningococcus meningitis is subjected to lumbar puncture. If the spinal fluid is cloudy, enough is removed to reduce the intraspinal pressure to an approximate normal and a less amount of serum is at once allowed to run into the spinal canal. If the spinal fluid is clear, no intraspinal injection is made. The fluid is immediately examined. Meanwhile the patient receives a desensitizing dose of serum. One hour later 50 to 120 cc. of serum are administered by vein, the first 15 cc. at the rate of 1 cc. per minute. Large glass syringes are used for this, as the flow is easily controlled and a cumbersome arrangement of tubes and stopcocks is not necessary. In a case of ordinary severity this intravenous dose is repeated every twelve hours until the tempera-

ture becomes normal, or until six or eight injections have been given. In severe cases the serum is repeated every eight hours. If meningitis is present or if it subsequently develops, intraspinous injections of serum are given and repeated once in twenty-four hours until the organisms disappear from the spinal fluid and lymphocytes make their appearance in numbers. In Herrick's experience with large intravenous injections of serum combined with intraspinous treatment meningococci disappear from the cerebrospinal fluid more rapidly than when intraspinous therapy alone is employed. Herrick believes that when antibodies are present in the blood stream removal of cerebrospinal fluid allows the passage of antibodies from the blood stream into the subarachnoid space. He states that he has seen no ill effects from these large amounts of serum intravenously. In 129 cases treated by Herrick by intraspinous method alone or with small doses of serum intravenously the mortality was 37 per cent. In 79 cases treated with large amounts of serum intravenously and average amounts intraspinously it was 16.4 per cent. In 138 cases reported by Golden the mortality was 21 per cent. It cannot be denied that the intravenous injection of serum is a logical procedure when the disease is recognized during the premeningitic stage of the disease, which is infrequently the case. The diagnosis at this stage of the disease is difficult to make and except in the midst of epidemics the vast majority of the cases are not recognized before the development of the meningeal symptoms. After this there is usually no bacteriemia. It is contended that the course of the disease is shortened and the mortality is reduced by the combined intravenous and intraspinous method of treatment. Whether this is so only in cases of meningitis with an associated blood infection or applies as well to cases of meningitis without organisms cannot be proven until more data become available. The great variation in the mortality during an epidemic in cases treated by the same methods makes one regard the statistics relating to the intravenous use of serum conservatively (chart 1).

Although Herrick states that he has seen no ill effects from the use of large doses of serum intravenously, other clinicians have not had such good fortune. Golden found that the intravenous injection of 20 to 40 cc. were usually followed by more or less shock with

failure of the pulse and respiration lasting about fifteen minutes, followed by chill and fever. The French clinicians, Sainton, Netter and Brules, while recognizing the theoretical advantage of intravenous serum, consider it a dangerous procedure and advise the use of intramuscular and subcutaneous injections. Although many writers refer to the reaction from the intravenous injection of serum, no fatal-

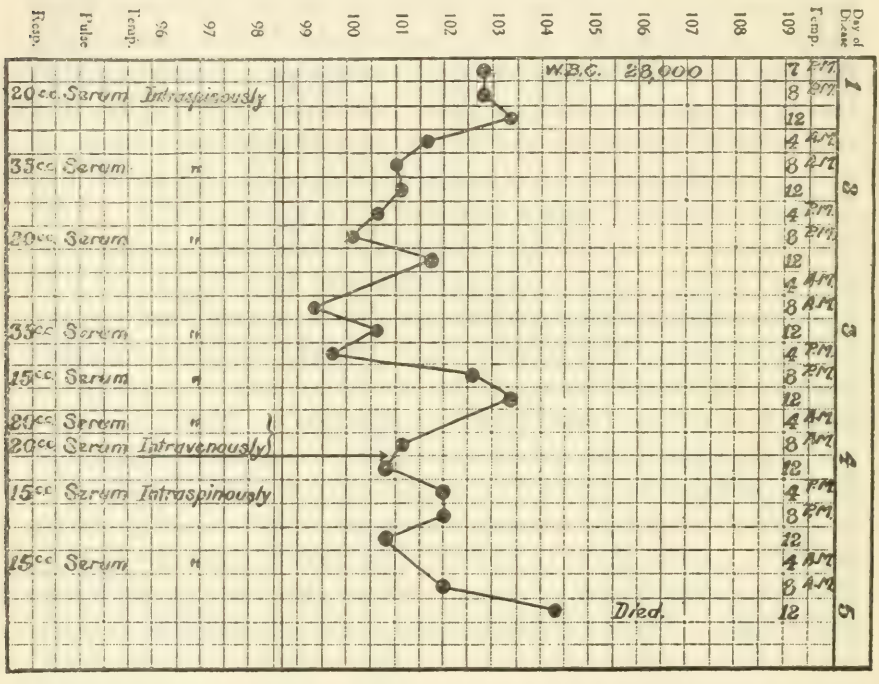

CHART I.

VERY SEVERE CASE. DEATH ON FIFTH DAY IN SPITE OF INTRASPINOUS AND INTRAVENOUS TREATMENT

ities have been recorded. I have seen two children whose death was apparently hastened by its use and for that reason I am inclined not to use serum intravenously except in specifically indicated instances. Intravenous serum therapy in meningococcemia alone or in those cases of meningitis in which the meningococcus persists or reappears in the blood stream is a rational and highly advisable procedure. A special serum freshly prepared and free from sediment

and preservative should, however, be prepared for intravenous use. Too great care cannot be taken in properly desensitizing the patient when serum is to be administered intravenously.

The question has recently been raised as to whether a preliminary lumbar puncture should be made in all cases where meningitis is suspected on account of the danger of producing a meningitis if there be an associated septicemia. Weed and his co-workers found that in animals the removal of cerebrospinal fluid during an artificial septicemia was followed by a localization of the infection in the meninges. Wegeforth and Latham report that the cerebrospinal fluid was normal in 55 out of 93 patients in whom meningitis was suspected and in whom lumbar puncture was done. Six of these patients at the time of puncture gave as positive blood culture and 5 of them subsequently developed meningitis. They are of the opinion that the logical procedure is to treat the blood infection and to avoid spinal puncture until signs of involvement of the meninges is evident. The experimental work of Flexner and Amoss, Austrian and others also shows that the introduction of a foreign serum favors the localization of the blood infection in the meninges. This question is one of practical clinical importance in the treatment of meningococcus meningitis. It seems imperative until we have a better means of recognizing meningococcus sepsis and an entirely accurate method beside lumbar puncture of excluding meningitis not to delay early lumbar puncture so that if meningitis is present patients may receive the benefit of serum at the earliest possible treatment.

Lumbar puncture in relation to the treatment of meningitis

Although the credit of perfecting the technique of lumbar puncture and of introducing it as a method for use in clinical medicine belongs to Quincke, the procedure was first employed by Corning in 1885 who injected various drugs into the lumbar subarachnoid space to induce spinal anesthesia. Wynter in 1889 also performed lumbar puncture to relieve the cerebrospinal pressure in patients with tuberculous meningitis. The first patient on whom Quincke performed lumbar puncture was suffering from hydrocephalus which had resulted from meningococcus meningitis. Since his admirable and complete study, lumbar puncture has been adopted generally in the

study and treatment of disease of the central nervous system. Puncture of the subarachnoid space is generally performed in the lumbar region as here the spinous processes are short and widely separated. The subarachnoid space is more spacious at this point than at the upper part of the spinal canal and there is no danger of injury to the cord. The site of election is between the fourth and fifth lumbar vertebrae, or on a level connecting the highest points of the iliac crests. At this point the subarchnoid space is entered below the conus medullaris through the comparatively thin layer of lumbar muscles. Punctures at other levels while less desirable may be made as high as the eleventh or twelfth thoracic vertebra or at the lumbosacral interspace below. Above the level of the eleventh interspace lumbar puncture is seldom successful, it may indeed be dangerous. Lusk found above this point that the posterior subarachnoid space was frequently obliterated by adhesions even in normal persons and that in this situation fluid could not be obtained unless the cord were perforated and the anterior subarachnoid space entered. From the time when Wynter in 1889 made a small incision along the spine of the second lumbar vertebra and introduced a Southey tube and trocar into the subarachnoid space many forms of apparatus, many of them elaborate, have been devised for this procedure. Simple instruments are entirely satisfactory. The needles measure from 3 to 10 cm. in length and from 0.8 to 1.6 mm. in diameter. They should be stiff but allow of a certain amount of flexibility. It should be possible readily to withdraw the stylet from the needle. The stylet should be beveled and flush with the end of the needle. The needle should have a short bevel and should be sharp so as to pass readily through the dura and not push it in front of it and thus prevent the flow of cerebrospinal fluid. Strict surgical asepsis is imperative. The needle and other apparatus should be boiled and the site of the puncture properly prepared according to the usual surgical methods. Great care should be taken to avoid secondary infection.

Lumbar puncture may be performed in either the upright or recumbent posture but in meningitis it is always the conservative plan to perform the operation in the recumbent posture. It is difficult to maintain patients in the upright position for as long a time as is necessary and there is greater danger from collapse. It is more

convenient to puncture adults in bed. Infants and children may be moved to a firm table or surgeon's carriage. The patient is moved to the edge of the bed or table on either side with the buttocks at the edge; the knees are flexed on the abdomen and the head and neck are bended forward so that the whole spine is flexed to its fullest extent. The patient must be maintained in the required position quietly and without struggling. As the position is a matter of the greatest importance in facilitating the operation, a competent assistant is necessary. Carelessness on the part of the assistant in maintaining the patient in the proper position is the cause of more unsuccessful punctures than is lack of skill on the part of the operator. With the patient in the proper position, the lateral or the median route may be selected to enter the subarachnoid space. In either route the anatomical landmarks are the same. The puncture should be made between the fourth and fifth lumbar vertebrae at a point about on a line drawn between the iliac crests. The spinous process of the fourth lumbar vertebra is located and the needle is inserted into the interspinous space next below this. In the median route the needle is inserted directly through the interspinous ligament and dura-mater. The depth of the puncture varies from 1 inch in children to 3 inches in adults. With experience a sense of touch is developed which indicates that the subarachnoid space has been entered. The median method is preferred with children. Many clinicians prefer the lateral method in adults as the firm interspinous ligament is avoided and nothing except soft tissues are met until the ligamentum subflavum is reached. The technique for this method given by Foster and Gaskell is as follows: The needle is held with the butt resting in the hollow of the palm, the shank steadied by the forefinger and thumb. A point is then selected mid-way between the fourth and fifth lumbar spines, $\frac{1}{4}$ inch laterally to the middle line, and preferably on the dependent side. The skin is steadied by the forefinger and thumb of the left hand. The needle is pushed toward the middle line, forwards and slightly upwards. Should the needle impinge upon the bone, it must be slightly withdrawn and the point directed lower down. If no bone is encountered, the point of the needle is felt to pass through the ligamentum subflavum, which gives the sensation of piercing gristle, and then through the dura mater. The piercing of the dura

mater has an entirely different feel, which has been described as being like passing a knitting needle through sacking. When the dura mater has been pierced, the needle can be felt free in the subarachnoid space. In either method the needle should not be pushed farther after it has pierced the dura mater, otherwise it may reach the body of a vertebra and injure one of the anterior longitudinal veins. Blood is then obtained. This is a much more frequent occurrence in children than in adults. Having entered the subarachnoid space, the stylet is removed and the cerebrospinal fluid is permitted to flow. The stylet should never be withdrawn completely until after a few drops of fluid have escaped so as to permit the cerebrospinal pressure to be lowered gradually rather than rapidly. After the first few drops the fluid for examination is collected in a sterile test tube. The amount of fluid withdrawn is determined by the rate of flow and the general reaction of the patient. Usually when the flow reaches a rate of one drop to every three seconds it indicates that about a sufficient amount has been withdrawn. The patient should be observed most carefully during this procedure. Headache, alteration in pulse and respiration are warnings that further amounts of fluid should not be withdrawn. Although Sophian has shown that the evacuation of cerebrospinal fluid in very large amount has but little effect on the blood pressure, I do not believe it is a wise procedure to withdraw the fluid completely. I have seen a number of patients suffer severe collapse by withdrawing too completely the fluid from the subarachnoid space. Manometers have been devised by Quincke, Kroenig, Crohn and others to indicate the sudden fall in cerebrospinal pressure but these are unnecessary if the pulse and respirations are watched and the fluid allowed to escape slowly and to run until it has reached the normal rate.

Lumbar puncture as a rule is a comparatively easy procedure but even in the hands of those who have developed a considerable degree of skill unsuccessful punctures occur not very infrequently, especially in infants and young children. The most common causes of failure to obtain fluid are that the needle has not been within the subarachnoid space, that it has not penetrated the dura or that it has been obstructed by a nerve. Rotating the needle or moving the needle slightly backwards or forward, reinserting and withdrawing the

trocar often are followed by a free flow of fluid. Sometimes the fluid may be so thick that it cannot flow through the needle. In such cases it may be impossible to obtain even a few drops of fluid. Small particles of exudate may obstruct the lumen. Reinserting the trocar or moderate suction by a syringe may obviate these difficulties. Blood in the spinal fluid may be due to the puncture of a small blood vessel in the subcutaneous tissue, or an injury to a branch of the venous plexus in the spinal cavity. Blood appearing toward the end of the collection of cerebrospinal fluid may mean that there has been a rupture of the capillaries within the subarachnoid space as the result of the relief of pressure. In exceptionally fulminating cases the cerebrospinal fluid is sometimes hemorrhagic.

A successful puncture in nearly all cases is possible but many times it requires great perseverance. It is questionable whether one should speak of a so called "dry tap." I have never seen but one instance in which fluid could not be obtained and that was in a patient with a congenital obstructive hydrocephalus from whom a meningocele had been removed. Even in obstructive hydrocephalus a certain amount of cerebrospinal fluid can be obtained.

As mentioned above, too rapid lowering of the cerebrospinal pressure seldom produces symptoms of shock or collapse. Incontinence of urine and feces, sharp pains along the thighs, headache, pain and weakness in the back, etc., sometimes follow the procedure but they are usually temporary. As in the case of lumbar puncture for spinal anesthesia, temporary paralysis of the bladder and anus and even paraplegias have been described following lumbar puncture and the introduction of serum. It is difficult in meningitis to account for these sequelae entirely as the result of lumbar puncture. The dangers from lumbar puncture itself are remote and for the most part with proper precautions may be disregarded.

As it is necessary during the course of the disease to make repeated punctures from day to day and often over a long period of time, the interspace entered should be varied from one puncture to another and every precaution taken to prevent secondary infection. With sterile technique the skin wounds seldom become infected.

The question of anesthesia during lumbar puncture has received considerable attention both in this country and in Europe. Some

authorities regard a general anesthesia as unnecessary while others advise either the use of a local or general anesthesia in all cases. Sophian regards general anesthesia as dangerous while Horder, Robb and others recommend its use in all cases unless the patient is unconscious or it is definitely contraindicated. A general anesthesia is to be preferred to local anesthesia as the discomfort of inserting the lumbar puncture needle as a rule is no greater than is that from the needle puncture used to inject the local anesthetic. The chief argument against a general anesthesia is that it further increases the dangers from the disease and as the discomfort from puncture is not excessive it is unwarranted with a procedure no more painful than lumbar puncture. With a patient who is delirious and struggling it is necessary, otherwise it would be impossible to keep the patient quiet and in position long enough to carry out the necessary treatment. Anesthesia may also be advantageously used with some patients who have to be repeatedly punctured on account of the fear of the operation. Anesthesia affords a sufficient amount of mental and physical relief to some adults to warrant its use but as a general rule the operation is accompanied by so little pain that it is not necessary. It is seldom necessary in infants and young children. Ether is probably the best and safest anesthetic to use.

The intraspinous administration of serum in meningitis

The successful treatment of meningococcus meningitis depends upon the early recognition of the disease and upon the early and efficient administration of antimeningococcus serum. It is essential that the serum should be of high potency and contain antibodies specific for the causative type of organism; that it be maintained within the cerebrospinal system at high concentration and in direct contact with the meningococci. Free drainage should be obtained from time to time by spinal puncture. There are also certain general and symptomatic measures that must be carried out in addition to the specific serum treatment.

Action of the serum

The chief action of the serum is doubtless due to bacteriolysins which destroy the organisms and in part also to those substances which

promote phagocytosis. For these reasons it cannot be too much emphasized that the serum used in the treatment of a given case of meningococcus meningitis must contain antibodies specific against the infecting strain of meningococcus. By examination of the cerebrospinal fluid in the course of treatment it is appreciated that the direct action of antimeningococcus serum is on the meningococci. These become reduced in number and become altered in size and staining property. They are more readily taken up by leucocytes and their growth is inhibited. The toxic products liberated by the death of meningococci are perhaps neutralized by the antiendotoxin in the serum if such a substance be found in the serum. The extracellular organisms diminish rapidly so that after the first or second injection of serum they are almost all intracellular, gradually they disappear altogether from stained smears. The viability of the organism also diminishes so that it is impossible to cultivate them. Sometimes even when seen in smears, they fail to grow on culture media. Levy has shown that the meningococcus disappeared from the cerebrospinal fluid in 114 cases after the intraspinous injection of serum as follows: After the first injection of serum it disappeared in 18 cases, in 33 after the second injection, in 35 after the third injection, in 14 after the fourth injection, in 9 after the fifth injection, in 4 after the sixth injection and in 1 after the eleventh injection. I found that in the majority of cases the meningococci disappeared after five injections of serum. In the following summary the number of injections of serum required to destroy the meningococcus as shown by culture and smears:

In 5 cases the organism disappeared after 1 injection
In 4 cases the organism disappeared after 2 injections
In 7 cases the organism disappeared after 3 injections
In 4 cases the organism disappeared after 4 injections
In 9 cases the organism disappeared after 5 injections
In 2 cases the organism disappeared after 6 injections
In 1 case the organism disappeared after 7 injections
In 1 case the organism disappeared after 9 injections

As the result of the reduction in number and the disintegration of the meningococci and the diminution in the number of leucocytes, the turbid or purulent cerebrospinal fluid gradually becomes clear.

But aseptic meningitis which may be caused by the introduction of a foreign serum may be sufficient to cause a certain amount of turbidity in the fluid until treatment is discontinued. The polymorphonuclear cells are finally replaced by mononuclear cells at first in increased number and eventually these are reduced within normal limits. At the same time the globulin content in the cerebrospinal fluid and the amount of cerebrospinal fluid diminishes progressively from day to day. The fluid in cases recovering from cerebrospinal meningitis may closely simulate, with the exception of the presence of bacilli, that found in tuberculous meningitis. It may be increased in amount and clear but may contain an excess of mononuclear cells and globulin and may even form a film on standing. It may require days or even weeks before the fluid becomes normal. Besides acting directly on and destroying meningococci and neutralizing the endotoxins liberated, antimeningococcus serum undoubtedly hastens the solution of the exudate.

Antimeningococcus serum should be injected directly into the subarachnoid space. The subcutaneous and intramuscular injection of serum in meningitis is valueless. Previous to the introduction of the gravity method by Heiman in 1908, serum was introduced into the meningeal spaces by means of a syringe. After the cerebrospinal fluid was withdrawn the syringe was attached to the lumbar puncture needle and the serum injected slowly and with very little pressure. The gravity method is the one of choice, however, as the serum runs in slowly and at a regular rate with no sudden and pronounced increase in intracranial pressure. The cerebrospinal pressure may be directly controlled by raising or lowering the level of the fluid in the gravity apparatus. Elaborate equipments for the introduction of serum by this method may be obtained but for practical purposes it is only necessary to have a graduated funnel with rubber tubing which is connected with the lumbar puncture needle by a close fitting metal attachment. After the cerebrospinal fluid has been withdrawn the attachment is made and the serum, which has been warmed to body temperature, is allowed to run from the graduated cylinder into the subarachnoid space, care being taken that all air has been expelled from the tubing. The rapidity of flow is regulated by raising or lowering the funnel.

Symptoms caused by the injection of serum

The injection of serum invariably causes severe, often agonizing cramp-like pains which radiate down the back of the legs, to the epigastrium or up the back. These pains usually begin as soon as the serum flows in and are due to the sudden rise in pressure and stimulation of the nerve roots. They can be lessened somewhat by allowing the serum to run in at first very gradually. Serum warmed to body temperature before injection causes less pain than when it is cold. The pains disappear shortly after the cessation of the injection and often before it is terminated. After the serum has been injected the stylet should be replaced and the needle left in place. By following this routine procedure the cerebrospinal pressure can be quickly lowered if any serious disturbances develop from the injection. After a few minutes the needle is withdrawn and the wound closed with a sterile dressing. It is advised that the foot of the bed be elevated in order to facilitate the flow of serum to the cerebrum and that the patient lie on his face so that the serum will be directed to the region of the optic chiasm. As it has been shown that dyes when injected into the lumbar subarachnoid space pass upward within a few minutes and are quickly distributed over the brain, these measures are not absolutely necessary.

Sophian in observations on patients and Carter in experiments on dogs have shown that the symptoms of collapse which fortunately are not frequently met with are due to a sudden increase of intracranial pressure and a resulting depression of the respiratory center. This sudden increase results from a too great pressure used in the injection of the serum, too rapid an injection or too large a quantity of fluid injected at one time. The first sign of danger is an alteration in respiration, the breathing becoming slow, shallow and irregular. Respiration may suddenly cease. Dilatation of the pupils and incontinence of urine and feces also occur. The heart continues to beat for a long time. In one of my patients to whom serum was being given by the syringe method the respiration ceased but the heart's action continued actively for over an hour. Lowering the intracranial pressure by removing some of the serum that had been injected and active respiratory stimulation were unavailing. Sophian

recommends that the injection of serum should be controlled by blood pressure readings and that a drop of 20 mm. of mercury in the blood pressure of an adult is a contraindication to the further injection of serum. This procedure may advantageously be used in adults but with children in whom blood pressure determinations at best are variable, it is unsatisfactory. By the use of the gravity method, allowing ten to twenty minutes for the serum to run into the cerebrospinal space, alternately raising and lowering the funnel so that the flow of serum is carefully regulated and watching the patient closely for signs of impending relapse, the dangers of intraspinous treatment are materially lessened. Should signs of collapse appear, the injection should be stopped at once, the apparatus disconnected and the serum allowed to drain out. Artificial respiration should be started and atropine and adrenalin should be injected in full doses. In animals Carter showed that the symptoms could be relieved immediately by the injection of cocaine.

Dosage of serum

Inasmuch as the serum acts directly on meningococci, the important indication is to inject as much serum as is consistent with safety. As there is no standard measurement of activity of the serum and as it is not known accurately how much serum is necessary to destroy the organisms and neutralize their effects, the dose is measured by volume. The chief objects of the intraspinous treatment are to relieve the intracranial pressure, to remove the infectious cerebrospinal fluid and to inject the bactericidal serum so that it comes into direct contact with the meningococci. It is the custom of nearly all clinicians to inject a smaller amount than the quantity of cerebrospinal fluid withdrawn. If 45 cc. of cerebrospinal fluid are withdrawn, it has been regarded as safe to inject 30 cc. of serum. In this way it is thought that there is no danger of increasing unduly the intracranial pressure. While in general this is a relatively safe rule to follow, it cannot be sufficiently emphasized that the injection must be made slowly and even when these precautions are observed, patients are occasionly met with in whom alarming symptoms result from the introduction of even small amounts of serum. As the result of Sophian's experience in controlling the dosage of serum by blood

pressure readings together with the clinical experience of many other observers, the following arbitrary standard of dosage according to the age of the patient may be generally considered safe:

1 to 5 years	5 to 15 cc.
5 to 10 years	10 to 20 cc.
10 to 20 years	20 to 30 cc.
20+ years	30+ cc.

However, it should be borne in mind that the dosage varies with each individual patient and that the volume of serum introduced should never be greater or as great as the amount of cerebrospinal fluid withdrawn. It is far better to inject an inadequate amount of serum and repeat the injection with no harm to the patient than to inject a larger dose with serious consequences.

In patients with thick plastic exudates and in those in whom only a few drops of cerebrospinal fluid can be obtained, the injection of small amounts of serum at frequent intervals, even under a certain amount of pressure, is compulsory for in no other way is it possible to introduce the serum and the danger of introducing serum in this way is less than allowing the patient to go untreated. In patients with a very thick cerebrospinal fluid which will not flow through the needle, two needles may be inserted at different levels and the canal irrigated with sterile salt solution. This sometimes sufficiently dilutes the cerobrospinal fluid as to allow it to flow and so permits the injection of larger doses. But even if free drainage can be established by repeated intraspinal injections the process is time consuming and irremediable damage, such as obliteration of the foramina between the ventricles and the cerebrospinal space, may be done in the meantime. Moreover, a very thick exudate means a very severe inflammatory process, the presence of a very large number of organisms and an urgent demand for early and intensive treatment. Intraventricular treatment is under these circumstances clearly indicated. The method of accomplishing this will be described subsequently.

An instructive example of what may be accomplished under such conditions are afforded by the following case:

The patient, three months of age, was admitted to the Harriet Lane Home on the third day of the disease, with a history of vomiting, fever, restless-

ness and convulsions. On physical examination there were the characteristic signs of acute meningitis and several small petechiae on the face. The temperature was 101.6°. As no cerebrospinal fluid could be obtained by lumbar puncture, a ventricular puncture was immediately done. The cerebrospinal fluid was cloudy and contained many polymorphonuclear leucocytes and numerous intra- and extra-cellular Gram-negative diplococci. The meningococcus was grown in culture. The blood culture was negative. Twenty cubic centimeters of serum were injected into the ventricle at once. Twelve hours later a few cubic centimeters of thick, turbid fluid showing meningococci were obtained by lumbar puncture. Five cubic centimeters of serum was injected under pressure with a syringe. On the following day, thirty cubic centimeters of serum was injected into the ventricle and although only a few cubic centimeters of cerebrospinal fluid was obtained by puncture, five cubic centimeters were again injected into the lumbar subarachnoid space by a syringe. At the time of the second lumbar puncture the spinal canal was irrigated with sterile normal salt solution but this did not have an effect on the amount of fluid which could be obtained. Phenolsulphonephthalein injected at this time into the lumbar subarachnoid space had not appeared in the ventricles the following morning. Thereafter thirty cubic centimeters of serum was injected into the ventricle and five cubic centimeters of serum was injected with a syringe into the lumbar subarachnoid space every twenty-four hours. The amount of cerebrospinal fluid removed by lumbar puncture slowly increased and after the seventh day thirty cubic centimeters of fluid was obtained. Phenolsulphonephthalein at this time flowed freely from the ventricle. The meningococci disappeared.

Frequency of injection

The frequency with which antimeningococcus serum is to be injected depends upon the severity of the infection and the duration of the infection before treatment is instituted. In a suspected case of meningitis lumbar puncture should be performed and if a cloudy fluid is obtained antimeningococcus serum should be administered without waiting for a bacteriological examination. Should the case eventually be shown not to be due to the meningococcus, no harm will have been done. In cases of average severity when seen within the first two or three days after the onset, the injection should be repeated every twenty-four hours for three or four doses. Hoher, Dochez, Debre and others have demonstrated that the serum is

practically all absorbed within twenty-four hours. No greater interval of time should therefore elapse between treatments. In cases of greater severity the injection should be repeated every eight or twelve hours for three or four doses and thereafter every twenty-four hours. This is for the reason that the activity of the serum may be exhausted in a short period of time even before the fluid portion of the serum is absorbed. The appearance of the cerebrospinal fluid at each puncture, the number of organisms and their relationship

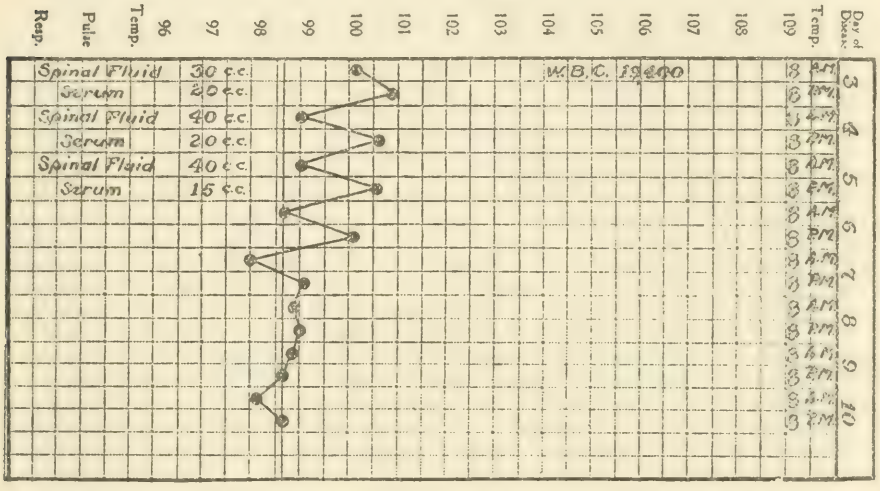

CHART II.

MILD CASE OF MENINGOCOCCUS MENINGITIS REACTING PROMPTLY TO INTRASPINOUS INJECTION OF ANTIMENINGOCOCCUS SERUM

to the leucocytes and their ability to grow upon proper culture media together with the general condition of the patient are the only safe and reliable indications to follow as to the frequency with which serum is administered.

Discontinuance of serum

In the average uncomplicated case of meningococcus meningitis, serum treatment is discontinued when the cerebrospinal fluid becomes clear and the organisms can no longer be demonstrated in smears or in culture. By this time also there is a general improvement in the

condition of the patient and the fever has usually nearly disappeared. With serum treatment the average duration of active symptoms is from eleven to fourteen days.

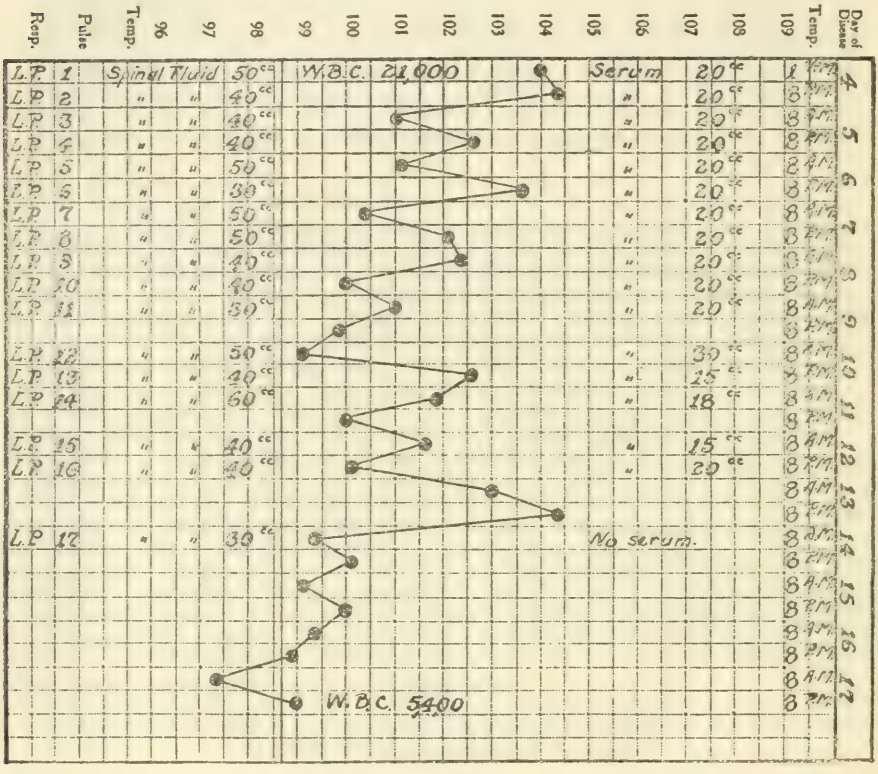

Chart III.

This Patient Required Intensive and Persistent Intraspinous Treatment

The spinal fluid, which would become apparently clear at one puncture, would at the next be very turbid and filled with organisms. Sixteen intraspinous treatments were required with a total injection of 320 cc. of serum before the spinal fluid became clear and meningococci disappeared.

Unfortunately the indications are not always definite and it requires sound judgment in determining when the injections are to cease. Although the general clinical condition of the patient as a rule may be relied upon as an indication, one often sees patients who are apparently recovering but viable organisms persist in the cerebro-

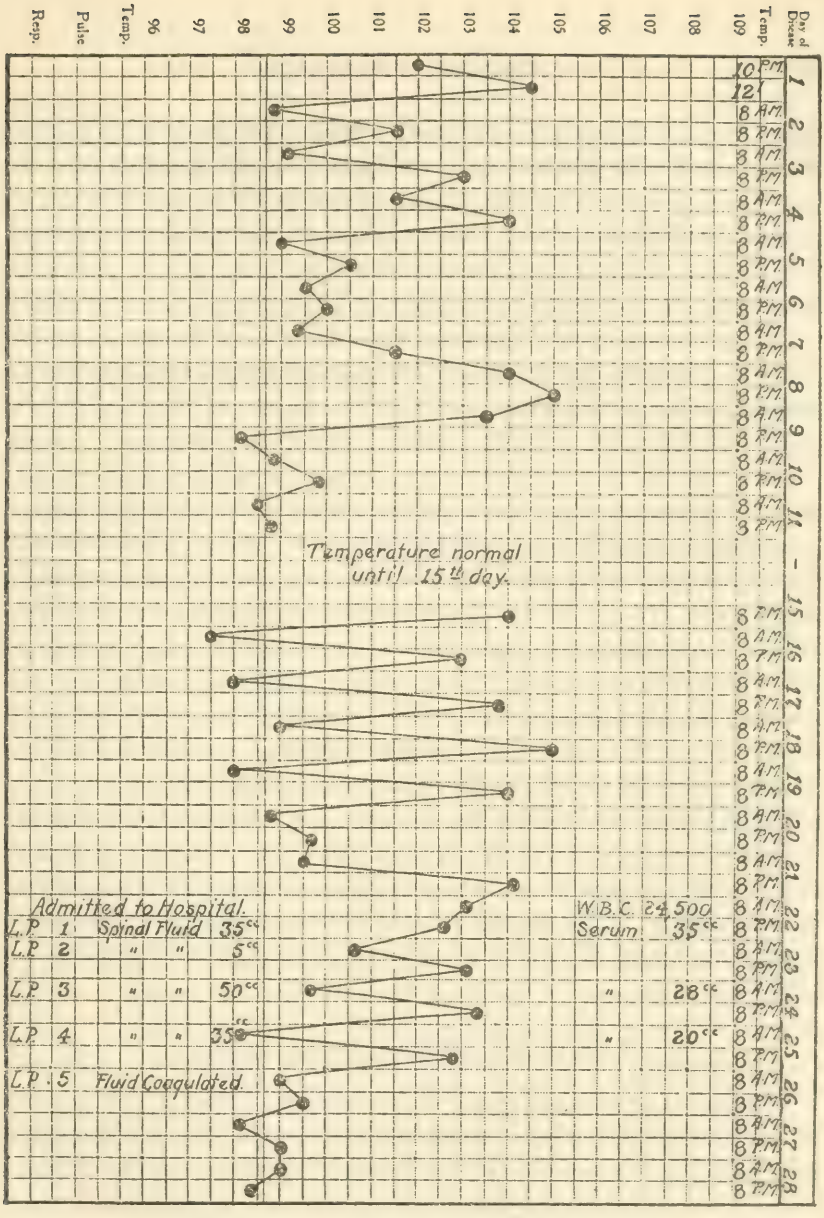

CHART IV.

CHARACTERISTIC FEBRILE REACTION IN AN UNTREATED CASE

While serum therapy is usually not very effective late in the course of the disease, it may at times bring about rapid cure. This patient was ill twenty-two days with an obscure fever, the cause of which had not been recognized. The temperature record had been kept. After 3 intraspinous injections of serum the patient made an uninterrupted recovery.

spinal fluid. The reverse is also often true. The patient may remain unimproved with persistence of the signs of meningeal irritation and yet the organisms cannot be demonstrated in the cerebrospinal fluid. The fever as a rule subsides with the disappearance of the organisms but it should also be remembered that irregular febrile paroxysms may often be caused by the injection of the foreign serum and in prolonged cases by the development of serum sickness. The only reliable criterion for the discontinuance of serum treatment is the disappearance of the organisms from the smears of the cerebrospinal fluid and their failure to be cultivated upon proper media. As the meningococcus grows slowly upon media it requires two or three days to be sure that a growth will not take place. When treatment is employed once in each twenty-four hours, two or three injections have thus been made after the cerebrospinal fluid is free from viable organisms. This is an added safeguard and produces no unfavorable effects. After that the character of the cerebrospinal fluid is followed by lumbar puncture at irregular intervals. Repeated lumbar puncture serves a double purpose in permitting cytological examination of the cerebrospinal fluid and relieving the increased intracranial pressure which frequently follows meningococcus meningitis.

Turbidity of the fluid is not an unfailing criterion for the continuation of treatment. The fluid may be free from organisms and yet contain so many cells as to be definitely cloudy or "ground glass" in appearance. The recent studies of Weed and his collaborators have shown the influence of the injection of foreign serum in bringing about such changes.

Early intraventricular injection of serum

In a series of articles which have recently appeared, Lewkowitz in discussing the serum treatment of meningococcus meningitis concludes that inasmuch as the lateral ventricles are the principal and essential seat of the infectious process, the meningococci spread from this focus throughout the entire subarachnoid space. He advises therefore that the serum should be injected into the lateral ventricles at the beginning of treatment and that daily injections in alternate sides or simultaneously on both sides should be made. In addition he recommends the use of vaccines. He describes the

method: The skull is punctured with a Götze grooved hand drill, 1.5 mm. wide. The needle is 1 mm. in diameter and 7 or 7.5 cm. long. A brass guide inside the needle prevents obstruction with tissue. The tip of the needle is not sharp, as the only obstacle it has to force is the dura. The puncture is made anywhere along the top of the skull, 3, 4 or 5 cm. from the median line, pointing the tip of the needle toward the center of the skull. The depth of the puncture should be about 40 mm. for infants, 50 to 60 mm. for older children, and 60 to 75 mm. for adults. The fluid should not be injected until the needle is certainly in the ventricle. This is proved by the fact that cerebrospinal fluid flows from the needle and by the drop in tension as the antiserum spreads in the ventricles. The tension should not surpass 60 to 80 mm. mercury for older children and adults, and 40 to 50 for infants. Lewkowitz advises therefore that a manometer with a three-way stopcock be interposed between the needle and the syringe. The injections are always made through a new opening. In the first series of cases which he reported the mortality was 36 per cent and this rather high mortality he accounts for on the basis of an inactive serum and fulminating types of cases. He warns against the use of horse serum for a period longer than 13 days on account of an anaphylactic reaction in one case. After the thirteenth of fourteenth day he is inclined to rely on the use of vaccines. He believes that all cases should be treated by the early ventricular injection of serum. Undoubedly this would be the procedure of choice were it definitely established that the organism gained entrance to the meninges by way of the ventricles. The weight of evidence in meningitis produced experimentally is against this view. Although the intraventricular injection of serum has its indications in small infants and in patients with a thick plastic exudate with or without hydrocephalus, the early injection of serum into the ventricles in the average uncomplicated case is not necessary.

Amount of serum used during the treatment

The amount of serum required in each individual case varies within wide limits and depends entirely upon the course of the disease. In one of my patients who was treated four hours after the onset of meningeal symptoms, only one injection of 20 cc. of serum was given

and was followed by rapid recovery. Netter, Worster-Drought and Kennedy and others have given as high as 600 to 800 cc. during the course of the disease without ill effects. It is not so much the amount of serum that is important as it is the quality of the serum and the time at which it is employed (chart V).

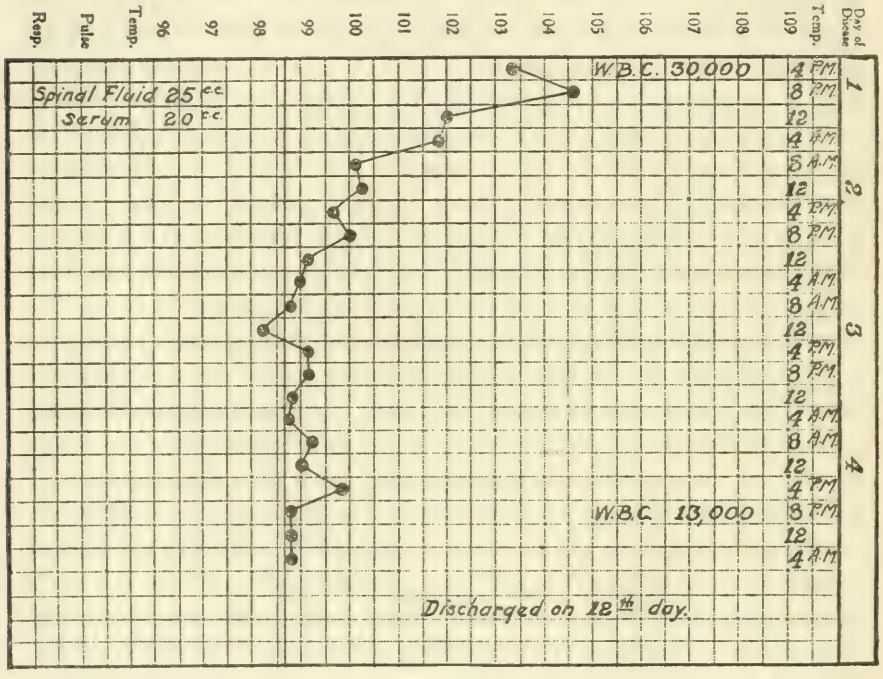

CHART V.

FIRST AND ONLY INJECTION GIVEN FOUR HOURS AFTER ONSET

Cerebrospinal fluid clear, containing many Gram-negative extracellular organisms. Complete recovery.

REINFECTION AND RELAPSES

The reappearance of meningococci in the cerebrospinal fluid either with or without the appearance of signs of meningeal irritation may take place even while serum is being given or after the discontinuance of treatment. These relapses are not nearly so frequent since the introduction of serum therapy but they occur in a small proportion of patients. Worster-Drought and Kennedy observed a relapse in less than 5 per cent of their cases. In my experience they have been

met with only in the cases running a chronic course and in the cases above referred to. They probably result from the fact that a certain number of organisms are walled off in patches of exudate which the serum cannot penetrate or else are contained in small superficial abscesses in the brain or cord. It is not always easy to recognize the beginnings of a relapse for it may occur with the onset of serum sickness and there may be strikingly few meningeal symptoms. A positive and early diagnosis of a relapse is only to be made by an examination of the cerebrospinal fluid. The treatment of a relapse is the same as the treatment of the original disease. The dangers from anaphylaxis in the treatment of relapse are considered under the heading of anaphylaxis.

During the course of meningitis there are certain symptoms that are in all probability the result of increased intracranial pressure or at least they are made worse by the pressure. These are headache, often agonizing in character, vomiting, retraction of the neck and some elevation of temperature. The mere removal of cerebrospinal fluid often brings about a distinct amelioration. These symptoms may be present sometimes to a marked degree, even after all meningococci have been killed and the serum treatment discontinued. They apparently depend upon the disproportionate production of cerebrospinal fluid due to a too rapid production or to a too slow absorption. The disease itself and the treatment by foreign serum may each be responsible for this condition of affairs. A rapid improvement results from lumbar puncture and the withdrawal of fluid but the symptoms may return again and again. It is imperative to continue the withdrawal of fluid until there is no return of any of the symptoms. This may require occasional lumbar puncture for several weeks. The following illustrates the results of repeated lumbar puncture after discontinuance of serum treatment (chart VI).

W. G., white, aged three years. Patient was admitted on the fifth day of the disease with typical picture of meningitis of severe form. Twelve intraspinous treatments with serum were given in the eight days following admission. No organisms were seen in smears from the spinal fluid after the ninth puncture. In spite of the apparently clear fluid he did not improve, the retraction of the head and the hyperaesthesia persisted, he was extremely restless and there was a coarse tremor of the extremities.

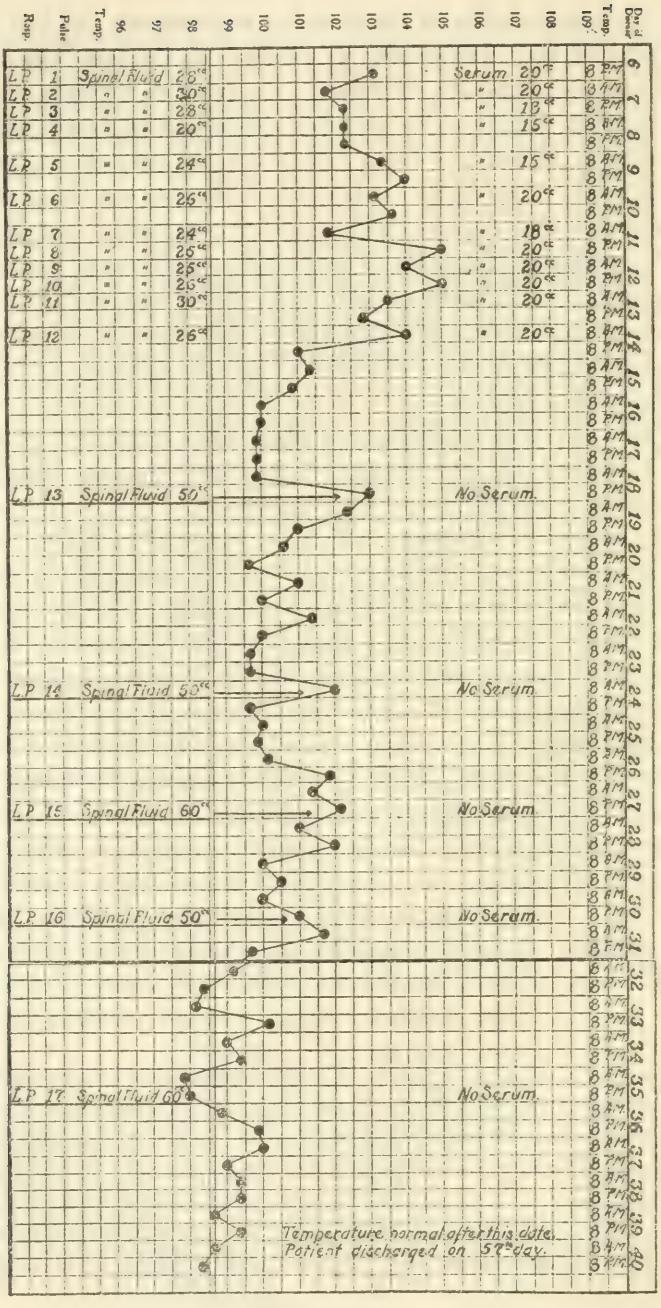

CHART VI.

REPEATED LUMBAR PUNCTURE AFTER DISCONTINUANCE OF SERUM TREATMENT

The eye grounds were normal. On the twelfth day the temperature rose to 103° and all the symptoms were exaggerated. A lumbar puncture was done and a large quantity of clear fluid containing no organisms spurted out under greatly increased pressure. There was marked relief following this procedure and the temperature fell. Thereafter, at intervals of about one week it was necessary to repeat the treatment. The symptoms were relieved each time by the removal of a large quantity of clear fluid. He was discharged as well on the fifty-seventh day of the disease.

Every one with experience in the treatment of meningococcus meningitis has seen alarming symptoms follow the injection of antimeningococcus serum. Death at times has followed treatment with serum so promptly that it is apparent that the treatment rather than the disease has been responsible. A number of views have been held as to the cause of these accidents. It has been claimed that the deaths were due to rapid lysis of the meningococcus and the consequent liberation of a toxic amount of bacteriotoxin, to the production through the introduction of large amounts of a foreign protein of anaphylactic shock, and to increased intracranial tension due to the too rapid or too free use of the antiserum. In 1912, Kramer advanced the view that cases of sudden death might be due to the presence in the serum of tricresol. Kramer injected a mixture of antimeningitis serum and a 0.5 per cent tricresol solution into the region of the fourth ventricle and directly into the subarachnoid space in dogs and as the result respirations were temporarily checked. One of the animals died after the injection of the serum into the subarachnoid space. Hall as the result of experiments also believed that tricresol is a dangerous preservative for serum which is to be introduced into the subarachnoid space and so come directly into contact with the nervous centers. He stated that death from the introduction of serum may result either from an increase in intracranial tension or from the presence in such serum of tricresol.

Flexner does not believe that the tricresol in antimeningococcus serum is responsible for the sudden deaths which have followed the use of serum. He points out that such deaths have been reported by Dopter using a serum which contained no preservative, also that there is no relationship between the conditions of the experiments and the conditions occurring in the subdural injection in human

beings, and that the injection of serum directly into the ventricle is not followed by serious symptoms. It is his belief that the alarming symptoms and death are most probably due to a rapid increase of the intracranial pressure occasioned by the injection of serum. That they can be avoided to a great extent by careful technique is evident from the experience of Sophian who reports some 1500 injections without a serious accident.

IMMUNITY CONFERRED BY ATTACK OF MENINGITIS

The degree of immunity conferred by meningococcus meningitis is apparently very small. Worster-Drought and Kennedy were able to demonstrate agglutinins in only 3 of 39 patients who had recovered from the disease. Authentic cases are reported in which "second attacks" occurred as early as 33, 45 and 73 days and as late as four and eleven months after the primary attack. It is probably better to consider such cases as relapses rather than second attacks. Although second attacks are rare, they do undoubtedly occur.

THE USE OF MONOVALENT OR POLYVALENT SERA

Since the recognition of the different types of meningococcus and the preparation of monovalent as well as polyvalent therapeutic sera, the procedure which is advised in the routine treatment of suspected or a proven case of meningitis has varied according to the experience of different writers. All are in accord that in a case of suspected meningitis if turbid or cloudy cerebrospinal fluid is obtained by lumbar puncture that a polyvalent serum should be administered pending the results of the bacteriological report. Whether treatment should be continued with a polyvalent serum of a monovalent serum is still the subject of much discussion. French observers at one time favored the injection of 20 cc. of antiserum A with 30 cc. of antiserum B until the type of the organism could be determined. Recently Nicolle, Debains and Jouan have prepared a bivalent serum made with organisms A and B, for immediate use prior to a bacteriologic diagnosis. After this they have advised the use of a monovalent serum according to the type of the infecting strain of meningococcus. In England a similar routine has been carried out and

as type I and type II are the most prevalent, a serum representing these two strains of meningococcus has been given at the first injection and after the causative strain has been determined, the corresponding monovalent serum has been given. The objection to the use of only bivalent serum is obvious. If there is difficulty in typing the organism a delay in using a highly potent serum might arise. But excellent results from the use of a monovalent serum have been reported from both England and France. The routine followed by Gordon and Hines is as follows: A bivalent serum made from type I and type II is used until the type of the infecting meningococcus is determined. Then the corresponding serum for the type of meningococcus found is given. Out of 83 cases, 34 were due to type I and the mortality was 3 per cent; 32 were due to type II and the mortality was 21.9 per cent. Ten were due to type III, no deaths, and 7 to unknown types and the mortality was 28.6 per cent. Out of the 83 cases the mortality was 12 per cent. The monovalent serum for type II is less effective than the sera for the other types for Gordon and Hines say that it contains less antiendotoxins for the homologous meningococcus than the other sera do. Sir Humphrey Rolleston observed a small outbreak of 10 cases due to type II. All of the patients died although treated vigorously both intravenously and intraspinously with a monovalent serum from type II organism. Munro used a pooled serum containing 50 per cent of antibodies to type II and a monovalent serum was used after the type was determined. He treated twelve consecutive cases of cerebrospinal fever in this manner and he says that in his experience no patient has died where it was possible to treat by monovalent serum. Recently a polyvalent serum has been used in this clinic in a few cases at the initial injection and thereafter the corresponding monovalent serum. The results so far have been sufficiently satisfactory but the number of cases treated have been too few from which to draw conclusions.

If it can be proved that the activity of a monovalent serum against the corresponding type of the meningococcus is greater than the activity of a polyvalent serum against the same organism, then it would seem logical to employ the monovalent serum after the type of organism has been determined. Unless this can be proved, there are great advantages in using the polyvalent serum. Studies from

the Hygienic Laboratory in Washington have shown the titre of the polyvalent sera to be as high as that of the monovalent sera that have been tested. At present therefore it would seem that for general use a polyvalent serum is preferable.

In all cases of meningococcus meningitis the type of organism from the cerebrospinal fluid should be determined by agglutination tests and a serum containing antibodies specific for that type of organism should be used. If the types of organism used in the preparation of the serum are not known, the agglutinating power of the serum toward the specific type of organism should be tested. Sera showing a low agglutination titre should not be employed. It is the universal opinion that the polyvalent serum prepared by the Rockefeller Institute has given better results than sera prepared at other laboratories. On account of the practical difficulty in making prompt and accurate type diagnoses, all antimeningococcus sera sold in interstate traffic in the United States are now required to be polyvalent with high titre against strains representing four different serological groups. These groups roughly correspond to those of Gordon, but are not perhaps identical with them. Sera now being made in the United States are from horses which have received intravenous injections of living meningococci. At least twelve different strains representing different types and variants sent out by the Hygienic Laboratory are used in its production.

DRUGS IN TREATMENT OF MENINGITIS

Drugs, except for the relief of symptoms, have proved valueless. Hexamethylenetetramine (Hexamine) since it was shown by Crowe to be excreted into the cerebrospinal fluid has been used extensively but apparently it has no influence upon the course of the disease. In 1914, Thomas Walker suggested the use of hexamethylenetetramine-anhydromethylene-citrate (Helmitol) as a substitute for hexamine inasmuch as it liberates formaldehyde in alkaline as well as in acid media. It has been shown that this drug exerted an inhibitory effect on the meningococcus in vitro and as a result of these experiments the drug was tried in the treatment of meningococcus meningitis. Given intravenously hemitol appears in the spinal fluid within half an hour and 15 grains administered by mouth could be demon-

strated in the cerebrospinal fluid within twenty-four hours. It was impossible, however, in any of the cases in which it was used to demonstrate the presence of free formaldehyde. Clinical results with this drug have been very unsatisfactory. Fairly and Stewart combined hemitol with normal saline or horse serum and injected this in 10 cases of meningococcus meningitis. Six of the 10 patients recovered. Besides the administration of hexamine and hemitol intravenously the arsenical preparations together with soamin have also been employed intravenously but without appreciable effect on the course of the disease. Soamin has been used principally in the East and was tried in meningococcus meningitis inasmuch as it has been thought to be of value in trypanosomiasis. Shiroore and Ross and Gilks and Butler have used the drug in British East Africa quite extensively. They reported its use by intramuscular injection in 127 cases. The mortality was over 50 per cent. Iodide of potassium and mercury and antimonium tartrate likewise have been used but without effect. The results reported by all writers show that there is little clinical or experimental evidence at hand to support the use of drugs in the treatment of this disease and they cannot be recommended unless combined with the use of antimeningitis serum.

OTHER MEASURES EMPLOYED IN TREATMENT

In the literature one finds, constantly, reference to other methods of treatment than the use of the specific serum. These methods have been tried either alone or in combination with serum. It is rather confusing to determine exactly the effects of these various added methods of treatment for the observations have not been sufficiently accurate or extensive to permit of a comparison between the cases treated with serum and those in which a combination of methods has been employed. It is an interesting commentary that even in spite of a proved specific therapy methods which have been discarded and regarded as valueless should be taken up from time to time and that beneficial results should be claimed for them. This, however, is constantly occurring in the treatment of other diseases besides meningitis.

Recently one of the earliest methods of treatment, venesection, has been revived. Fairly and Stewart contend that in the acute

cases in which there are symptoms of respiratory failure, venesection combined with the application of cold compresses is beneficial. They also caution against the use of lumbar puncture in comatose patients, particularly if respiratory failure is imminent.

Long before the days of serum treatment various antiseptics were recommended and used intraspinously. In 1902 Seager recommended the use of lysol as a means of combating the disease and in 1904 Manges tested its effects upon a number of patients. Wolff as a result of the recovery of 5 out of 8 patients whom he treated with the intraspinous injection of protoargol recommended this substance and said although its curative value had not been proved, that it can be injected in the subarachnoid space without harm. In 1916, Flexner and Amoss presented the results of their experiments with lysol and protoargol in the treatment of meningococcal infections in guinea pigs and monkeys. They found that these substances possess none of the properties which are essential for combating meningococcus infection. On the other hand, they showed that the use of such drugs might have a harmful effect when combined with serum treatment inasmuch as they prevent leucocytosis and inhibit the phagocytosis of the organism. Carbolic acid, flavine and eusol and many other antiseptics have likewise been recommended for intraspinous treatment. The consensus of opinion is that there is no favorable influence from the injection of other substances than antimeningococcus serum upon the course of the meningococcus meningitis.

As a result of their experiments regarding the antibactericidal properties of human serum MacKenzie and Martin in 1908 injected from 15 to 20 cc. of fresh human serum into the spinal canal of 16 patients with meningococcus meningitis. Ten of these patients recovered. Since then a relatively large number of cases have been reported in which either the patient's own serum or convalescent serum has been used intraspinously in the treatment. Both favorable and unfavorable results have been reported, but on the whole the use of human serum has not been followed with brilliant results. Fairly and Stewart as well as Kolmer and his collaborators have endeavored to reinforce the complement activity of antimeningococcus serum by the addition of human and of rabbit serum. In Fairly and Stewart's cases thus treated the mortality was about 30 per

cent whereas in cases treated with serum alone the mortality was 50 per cent.

Much dissatisfaction with the results of serum treatment was expressed in England during the early months of the war and for a time the medical authorities were unable to decide how much benefit was derived from the intraspinous injection of antimeningitis serum and how much from the associated puncture. Indeed some authorities stated that in their opinion the old method of lumbar puncture and drainage without serum was the better form of treatment. As is well known, the explanation for the failure of serum was found when it was shown that the strains of meningococci causing the infection were in the majority of cases different from those used in preparing the antimeningococcic serum that was employed. As a result of this experience, however, numerous reports have been made regarding the beneficial effects of repeated lumbar puncture without serum administration. Olitsky in an epidemic in Southern China in 1918 had the opportunity of seeing cases which received no treatment and those in which lumbar puncture alone was performed. The mortality rate without treatment in 104 cases was 84.6 per cent, with repeated lumbar puncture in 346 cases it was 54.1 per cent. On the other hand, a number of authors have reported most unsatisfactory results from the use of repeated lumbar puncture without serum. This has been true not only during recent epidemics but in the treatment of the disease before serum treatment. In general, it would seem that by lumbar puncture alone the mortality from meningococcus meningitis can be reduced to a very slight degree, if at all.

Farmachidis has recently reported the successful employment of a normal salt solution in rinsing out the spinal cavity in a patient with meningococcus meningitis. He employed 360 cc. daily for twenty-five days. He would first withdraw 30 cc. of cerebrospinal fluid and then inject the same amount of salt solution. After a few minutes this was aspirated and allowed to flow out and 30 cc. were injected again. This was repeated 10 or 12 times at a sitting or until the cerebrospinal fluid finally came away clear. The cerebrospinal fluid became and remained clear after the twenty-third day. Aubertin and others have employed the same treatment. In my experience this method has not been attended with satisfactory results.

VACCINES IN TREATMENT OF ACTIVE STAGES

Meningococcus vaccines as a curative measure were employed but little before the war. In the epidemics following 1915 they have been used by a large number of workers and there is a considerable literature on the subject. Inasmuch as they have been used for the most part in conjunction with other remedies such as serum and repeated lumbar puncture, their usefulness is rather difficult to determine. Sophian referred to their use in 1913 and stated that in certain cases they may be more efficacious than serum. Rolleston refers to 32 cases treated with autogenous vaccines together with serum or soamin in which there was a mortality of 25 per cent. Many of his cases were recovering but vaccines did not seem to alter the course of the severe infections. Worster-Drought and Kennedy report in detail several cases which apparently were favorably influenced by vaccine treatment in conjunction with serum therapy. Chalmers and O'Farrell report a case of recovery from severe and protracted meningitis with septicemia. They discontinued serum treatment and ascribe the cure to an autogenous vaccine. They advise the use of vaccine with serum therapy in all cases from the onset. Horden reports the case of a seven year old child to whom vaccine was given on the thirty-ninth day and after six days the temperature fell to normal. A relapse occurred two weeks later and vaccine again seemed to influence the disease as recovery took place. Crowe also speaks of vaccines as having a favorable influence on the temperature. Fairly and Stewart say that it is not uncommon to see a patient who has been having an irregular fever become afebrile shortly after vaccines are given. Out of 52 chronic cases they had a mortality of 32 per cent. Lewkowitz urges their early use and says that they tend to induce a general immunization which is a potent aid in the cure. Colebrook believes that they increase the antibactericidal content of the blood and so increase the value of the serum in its action against the meningococcus in the cerebrospinal fluid. Nearly all workers advise the use of an autogenous vaccine but when it cannot be obtained, a polyvalent vaccine containing the representative strains of meningococci may be substituted. The dosage advised has varied considerably. Worster-Drought and Kennedy inject 250,000,000 organisms subcutaneously at some time

during the first three days and gradually increase the dose, 500,000,000 a dose, up to 2,500,000,000. The dose is modified for children. If there is a reaction to a particular dose, the same dose is repeated four days later. Walker-Hall gave a polyvalent vaccine in increasing doses from 25,000,000 to 500,000,000 every two days. Boidon gives from 200,000,000 to 750,000,000 every four days and MacLagan advises from 50,000,000 to 100,000,000 for the first dose. For the most part vaccines are recommended in the subacute or chronic stages of the infection when serum seems to become inefficient. In the acute cases but little benefit has been reported. No harmful effects with the exception of a temporary febrile reaction have been observed. Although the efficacy of vaccine therapy is not clear owing to its combination with other forms of treatment, until more information is available it would seem from so many favorable reports that in the subacute and chronic types of meningococcus infection this mode of treatment is worthy of trial.

As in other diseases for which there is a specific therapy certain general and symptomatic measures must be carried out in the treatment of meningococcus meningitis. The patient should be kept isolated in a quiet room or if in a hospital ward the patient should be separated from his fellow patients by a screen. The room or ward should be provided with an abundance of fresh air. Careful nursing is of the greatest importance particularly for delirious patients or those who are in coma. Much can be done to relieve the suffering of patients who are in a state of rigidity. Changing the position from time to time and supporting the head and knees with pillows will not only add to comfort but does much to prevent the development of hypostatic pneumonia and bed sores in those patients with a severe and prolonged form of the disease. The throat and nasal passages should be cleansed frequently with antiseptic washes and the eyes irrigated twice daily with boric acid solution. The diet is regulated according to the condition of the patient and every effort should be made to supply the patient with an adequate diet. A liquid diet is advisable during the acute stage. In unconscious and delirious patients feeding with a nasal tube or stomach tube must be employed. In patients with severe toxemia, water must be supplied freely. If there are evidences of desiccation, dryness of the skin and

mouth, loss of tone in the skin or a great diminution in the amount of urine, salt or glucose solutions may be given intravenously, subcutaneously, by rectum or directly into the peritoneal cavity. I have seen several children during the acute stages of meningitis who were greatly improved after several intraperitoneal injections of normal saline. This method has been described by Blackfan and Maxcy.

It has been found experimentally by Weed and McKibben that the volume of the brain can be controlled by a change in the concentration of certain elements in the blood stream. They showed that the intravenous injection of hypertonic solutions of certain electrolytes and crystaloids causes a transient rise in the pressure of the spinal fluid which is followed by a marked fall which persists for a considerable period of time. With this idea in mind Hayden treated two patients by means of the intravenous injection of a 25 per cent glucose solution and thought that the favorable outcome was partly the result of a decrease in the intracranial pressure brought about by a change in the bulk of the brain. Hayden advises the intravenous injection of a 25 per cent glucose solution, as a routine measure every twelve hours from the onset of the disease until there is no longer any evidence of increased intracranial pressure. Rest is essential and should be secured by the use of morphine or other sedatives. Relief from headache, vomiting and other intracranial pressure symptoms are best relieved by repeated lumbar puncture. Symptoms of cardiac and respiratory failure should be combated with atropine adrenalin, camphorated oil and citrated caffeine in full doses administered intramuscularly.

HYDROCEPHALUS

Early in the history of meningococcus meningitis it was recognized that "the disease was distinguished by the slowness of its cure and that its duration might be a matter of several months." Unfortunately this is true and while recovery from the infection may take place, irremediable permanent damage may have occurred.

One of the most frequent of the sequelae is hydrocephalus. It has been customary to speak of the manifestations of increased intracranial pressure which are seen at the onset and throughout the course of the disease as symptoms of acute hydrocephalus. We know

that these symptoms are largely due to the increased amount of cerebrospinal fluid which results partly from the stimulation of the choroid plexus and partly from the inflammatory process in the meninges which cannot be sufficiently rapidly removed by absorption even though this is but little interfered with in uncomplicated cases. There is a certain justification for speaking of acute hydrocephalus in some cases for the exudate may be so thick as partially or completely to obstruct for a time the foramina of exit from the ventricles. With time, especially when serum is used, this exudate frequently disintegrates and disappears and thus the channels of communication between the ventricles and the subarachnoid space are reestablished.

In patients never treated with serum chronic hydrocephalus is the most common of the sequelae and even in those actively treated by serum it results in a small but regrettable number of instances. This is especially the case with children. Hydrocephalus causes most of the striking symptoms seen in the subacute or chronic types of meningitis the rigidity of the limbs, the opisthotonos, the periodic vomiting, the peculiarity of the cry, the change in mentality and the enlargement of the head. The hydrocephalus is caused in the majority of instances by partial or complete blockage of the foramina Magendie and Luschka at the base of the brain or by obliteration of the cisternae (magna, interpeduncularis and pontis). The spinal subarachnoid space may also be more or less obliterated. In any event the free distribution of the cerebrospinal fluid throughout the cerebra and spinal subarachnoid spaces is prevented and its normal absorption is interfered with. Consequently there is an accumulation and retention of the cerebrospinal fluid within the ventricle. Anatomically, two types of hydrocephalus have been demonstrated: (*a*) the obstructive, and (*b*) the communicating. Obstructive hydrocephalus develops because the cerebrospinal fluid cannot pass from its place of origin in the cerebral and spinal subarachnoid space where absorption takes place. Communicating hydrocephalus—the channels of communication between the ventricles and the spinal subarachnoid spaces being patent to a greater or less degree—results because the cerebral subarachnoid space where the greater part of absorption takes place is partially or completely obliterated. In the majority of instances it is due to adhesions which obliterate the various cis-

ternae or centers and obstruct the foramina. A combination of the two types of hydrocephalus may result if there is partial obstruction to the foramina and partial obliteration of the cisternae.

Attention must be directed to a hydrocephalus developing in meningitis by the onset of certain symptoms. The diagnosis is readily established when the condition is of long duration and the symptoms of increased intracranial pressure—headache, stupor, vomiting, enlargement of the head and changes in the eye grounds—are present. The early manifestations of hydrocephalus, however, are so closely interwoven with the symptoms of the meningitis itself that they are often difficult to recognize. Hydrocephalus should always be suspected with the persistence of symptoms of meningeal irritation (fever, hyperesthesia, irritability or drowsiness, rigidity of the muscles of the neck and extremities, hyperactive reflexes, tremors, etc.) or their reappearance after the symptoms of meningitis have subsided. Infants invariably have a tense and bulging fontanel and in older children and adults Macewen's sign is positive. It should be remembered that these symptoms cannot always be referred to the hydrocephalus alone.

Lumbar puncture yields the most information regarding the development of hydrocephalus, though it is not absolutely dependable. In hydrocephalus the cerebrospinal fluid is under greatly increased pressure and either an abnormal amount is readily obtained or it is obtained in small amount and with difficulty. A definite increase in the amount of cerebrospinal fluid of 50 cc. or more, withdrawn repeatedly when the other signs of the acute infection of the meninges have subsided, is significant of a communicating hydrocephalus. In obstructive hydrocephalus a large amount of cerebrospinal fluid may be recovered at the first lumbar puncture and then the quantity lessens so that only a few drops are obtained at successive punctures. Corroborative evidence of the presence of hydrocephalus may be shown by the results from puncture of the ventricle, as in such cases the cerebrospinal fluid in the ventricles is under increased pressure and an excessive amount can be withdrawn. During the acute stages of meningitis a small amount of fluid obtained by lumbar puncture suggests an obstructive hydrocephalus, for if the subarachnoid space has been entered and the fluid is not too thick to run through the

needle, the prevention of a free flow of cerebrospinal fluid from the ventricles to the spinal subarachnoid space can hardly be caused by anything else than a thick exudate so situated as to obstruct the foramina of exit applied from the ventricles.

The differentiation between the two types of hydrocephalus by clinical signs alone, however, may be very difficult and for that reason I have employed in a number of cases the phenolsulphonephthalein tests used by Dandy and Blackfan in their study of chronic hydrocephalus. When phenolsulphonephthalein is injected into the ventricle in obstructive hydrocephalus, the dye does not appear in the cerebrospinal fluid obtained from the lumbar subarachnoid space within forty minutes, if at all. In patients who do not have hydrocephalus and in those with the communicating type of hydrocephalus, the phenolsulphonephthalein appears promptly (in from six to twelve minutes). When phenolsulphonephthalein is injected into the lumbar subarachnoid space in communicating hydrocephalus, absorption of the dye is greatly lessened. Less than 20 per cent is excreted in the urine within two hours, as compared to 35 or 60 per cent in normal persons. In obstructive hydrocephalus, when the cisternae and the meninges are not affected, absorption is as prompt as in normal individuals. In 17 cases of meningococcus meningitis communicating hydrocephalus developed in 8 patients and obstructive hydrocephalus in 9 patients. Ten of the 17 patients died. Two of the other 7 patients had an obstructive hydrocephalus and improvement followed promptly after the introduction of serum into the ventricles. The process in the 4 patients with communicating hydrocephalus became arrested after treatment. One patient with communicating hydrocephalus developed a chronic hydrocephalus in spite of the intensive intraventricular and intraspinous administration of serum.

Whenever in the course of meningitis fluid is obtained with difficulty or after temporary improvement there is a reappearance of the symptoms of meningeal irritation (hyperesthesia, vomiting, drowsiness, increased rigidity, etc.), or when in spite of active treatment improvement does not occur, an obstruction to the free passage of fluid from the ventricles and into the cisternae of the subarachnoid space is to be suspected. This not only leads to hydrocephalus but prevents

the serum when injected below from reaching the inflammatory processes in the ventricles and over the surface of the brain. The injection of serum directly into the ventricles is then indicated.

INTRAVENTRICULAR INJECTION OF SERUM

The injection of serum directly into the ventricles was first employed by Cushing and Sladen. Since then it has been in rather general use. It is inadvisable to delay making use of this method. It should be resorted to in severe and complicated cases much more frequently than it has been in the past. Improvement may often and often does follow one or two injections of serum but repeated injection may be necessary. The dangers attending ventricular puncture are insignificant; in children it is oftentimes much easier than lumbar puncture. In infants the method of procedure is as follows: The patient should be wrapped in a blanket and placed in the recumbent posture on a table. The head must be firmly supported. An area corresponding to the anterior fontanelle having been shaved and the skin sterilized, the anterior fontanelle is outlined and an ordinary lumbar puncture needle with stylet is introduced just to one side of the mid-line to avoid the longitudinal sinus. The needle is pointed in a direction forward and slightly outward on a line with the optic foramen, and is pushed in to a depth of about $1\frac{1}{4}$ inches (3 cm.). When the ventricles are much dilated and the cerebral cortex thinned, the needle entering in almost any direction will usually find fluid. In older children and adults the method of trephining as devised by Keen or Kocher may be employed. It is always advisable to withdraw by aspiration large quantities of cerebrospinal fluid. Far larger amounts of serum can be introduced without danger into the ventricle than by the intraspinous route. It is preferable to enter each ventricle on alternate days but in the cases requiring trephine it has been our custom to inject through a single opening. Complete drainage of both ventricles can be accomplished easily by changing the position of the head during the process. Care should be observed when one opening is used that there is free communication between the ventricles. Cases have been reported in which the exudate has blocked the foramina of Munroe and under such circumstances the serum would not circulate freely within the ventricular

cavities. Various surgical procedures having for their objective continuous drainage have been employed but such methods offer no improvement over the method of ventricular puncture, with serum administration during the period of acute symptoms.

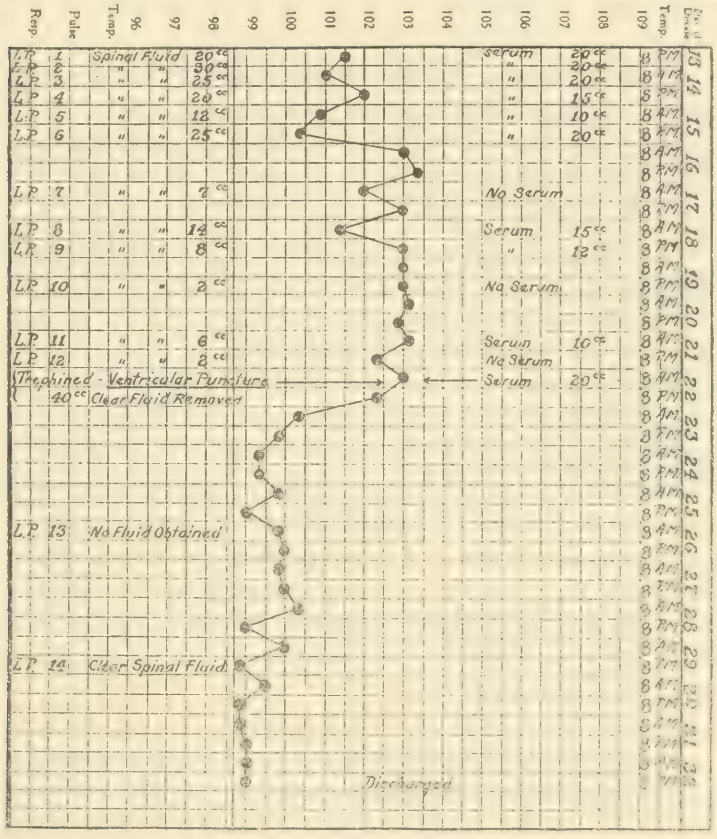

CHART VII.

SLIGHT IMPROVEMENT WITH INTRASPINOUS THERAPY BUT IMMEDIATE CURE WHEN COMBINED WITH INTRAVENTRICULAR TREATMENT

OTHER LOCATIONS RECOMMENDED FOR THE INJECTION OF SERUM

The introduction of fluid in other locations in order to overcome obstruction has been attempted by different clinicians. Chartier, Cantas, Ravaut and Krolunitsky and Netter have injected serum

in the dorsal and cervical regions. Punctures of the subarachnoid space in these locations were followed in some of their patients by convulsions. A patient so treated by Cantas recovered. Cazamian treated three patients by the injection of serum through the orbitosphenoidal route. One patient recovered. The technique of sphenoidal puncture is as follows: A pointed trocar and cannula is introduced at a point 2 mm. from the supraorbital notch, the trocar is then pushed slightly upwards and inward to reach the bony vault of the orbit. The pointed trocar is withdrawn and a blunt one substituted. By a little probing the most external portion of the sphenoidal fissure is reached. A fibrous membrane is pierced. The trocar, the inner end of which is in contact with the base, is then withdrawn and cerebrospinal fluid escapes. Serum is then injected through the cannula left in position.

Wegeforth and co-workers have used the space between the occiput and atlas to obtain cerebrospinal fluid from animals and believe that it may readily be used in man. They state that by this procedure specific therapy could be given more efficiently in early meningitis and indicate that it should prove of value in reaching the upper fluid reservoirs of the central nervous system when the spinal subarachnoid space is blocked. At the present time the method is the most satisfactory that has been devised when there is obstruction and when for any reason serum cannot be injected directly into the ventricles. Whether it has an advantage over the ventricular route remains to be determined.

In the chronic form of hydrocephalus after adhesions have taken place and when viable organisms cannot be demonstrated, the process cannot be further influenced by the injection of antimeningococcus serum. In the communicating type of hydrocephalus repeated lumbar puncture may be tried in the hope that the removal of large amounts of cerebrospinal fluid at regular intervals will retard the further development of the hydrocephalus until an equilibrium between the production of cerebrospinal fluid and its absorption is established. Although this does take place in a small percentage of cases, repeated lumbar puncture should only be tried temporarily, as permanent relief by more radical surgical methods cannot be expected if the hydrocephalus has reached an advanced degree. In obstructive

hydrocephalus early surgical interference is indicated. Operative measures for the relief of chronic hydrocephalus heretofore have been uniformly unsuccessful. It is hoped that by the methods devised by Dandy successful results will be secured for the relief of this otherwise hopeless sequela of meningococcus meningitis.

OTHER COMPLICATIONS AND SEQUELAE OF MENINGITIS

To those who have had experience with meningitis before and after the introduction of serum treatment, it is very evident that by serum treatment the complications and serious sequelae have been greatly reduced. Statistics bear this out. Recovery in the great majority of cases treated is complete. Flexner states that formerly there were sequelae in about 20 or 25 per cent of the 25 per cent of patients that recovered from meningococcus meningitis. In the recent epidemics with serum treatment they have been reduced to about 6 per cent.

Worster-Drought and Kennedy have collected the more serious sequelae which have occurred in 120 patients from two months to one year after recovery. Their summary follows:

	cases
Strabismus	2
Blindness (One eye)	1
Monoplegia (Function restored 7 months after recovery)	1
Hemiplegia (Function restored 7½ months after recovery)	2
True neurasthenia	4
Deafness	2
Deafness partial	1

Of 94 patients in military service 11 were discharged because of the following sequelae:

	cases
Neurasthenia	5
Deafness	2
Strabismus	1
Blindness	1
Residual weakness of 1 foot after hemiplegia	1
Persistent pain in lumbar region on exertion	1

According to Flexner's figures in the preserum period deafness was found in 12 to 33 per cent of the cases recovering. Among the serum treated cases it occurs in only 3.5 per cent. Deafness of central origin resulting from meningococcus meningitis is an early symptom and when it occurs it is almost always permanent. It is not influenced by treatment.

Eye complications are less frequent and take the form of a conjunctivitis, a severe uveitis, panophthalmitis and optic atrophy. Four to 6 per cent of the cases formerly developed eye complications. In Flexner's series the incidence was only 1 per cent. Uveitis may be and usually is followed by a panophthalmitis. As loss of vision is the usual sequel, the drastic method of the early intravitreous injection of serum has been advised. Netter reports two cases in which this was followed by improvement and the preservation of sight. Optic atrophy resulting from hydrocephalus is permanent and incurable.

Arthritis as a complication of meningococcus meningitis has been recognized for many years. Herrick and Parkhurst and Sainton have recently reported series of cases of arthritis which they have observed in recent epidemics. They found that arthritis not only might be associated with meningitis but it might be associated with meningococcaemia apart from a meningitis. A distinction has to be made between the arthritis resulting from meningococcus infection and that which occurs with serum sickness. Symptoms of arthritis depending upon an infection may occur at the onset of the disease or they may appear as late as the fifth or sixth day. The swelling may be great but there is always a striking disproportion between the amount of swelling and the other signs of inflammation, redness and pain, etc. Cure is usually spontaneous. The injection of serum directly into the joint in severe cases has been advised.

In the subacute and chronic stages of meningococcus meningitis, a secondary bronchopneumonia frequently occurs as a terminal event. Most frequently it is due to the pneumococcus, streptococcus or staphylococcus aureus. It is not unusual to recover the meningococcus from the sputum and from the lungs postmortem in such cases. That the meningococcus may produce a fatal pneumonia has also been recognized. Holm and Davison, as the result of their studies of pneu-

monia in France found that the meningococci present in the lungs in cases of meningococcus pneumonia were essentially the same type of organisms as those present in the cerebrospinal fluid. They showed that the organism may produce either a lobular or a lobar pneumonia with or without a meningitis. Treatment with serum intravenously or with vaccines should be tried in such cases.

Other complications such as pericarditis, myocarditis, endocarditis, pyelitis, cystitis, paralyses, etc., are to be treated according to the usual methods.

In the convalescent period of meningococcus meningitis various symptoms may appear. These are paralyses, irritability, pain, weakness and stiffness of the back, mental impairment, neurasthenia, etc. There is often awkwardness in walking and even paralysis of the bladder and rectum have been reported. Much attention has been directed to these symptoms since the introduction of serum treatment. It has been considered by some authors that these symptoms are the direct result of the repeated lumbar punctures and the injection of antimeningococcus serum. Whether they are or whether they are sequels of the disease itself it is hard to determine. Some writers have maintained that lesions of the cauda equina are responsible for many of the symptoms. Worster-Drought and Kennedy carefully examined 120 patients who had recovered from meningitis for evidences of such lesions. The number of punctures which had been performed on the patients varied from four to thirty-five. In no case were there any areas of anesthesia corresponding to the distribution of the fourth and fifth sacral nerves. Worster-Drought and Kennedy believe that pain and weakness in the back are a sequel of the disease and are not dependent on the punctures and administration of serum. Fortunately the symptoms that have been described are relatively rare. They are more common with adults than with children. They may disappear early in convalescence or they may persist for weeks or months. Recovery is usually complete.

SERUM DISEASE

The manifestations of serum disease in general that follow the injection of antimeningococcus serum are much the same as those

that follow the injection of any therapeutic sera made by immunizing horses. It was believed at one time that the manifestations were more frequent after the intraspinous injection than after the intramuscular or subcutaneous injection of serum but Rolleston and Kerr are of the opinion that this has not been proven. The incidence of serum sickness is influenced by the source of the serum as it is well known that serum from some horses is more apt to provoke serum sickness than that from others. The amount of serum injected may have some influence upon the incidence of serum sickness. Longcope and Rackemann believe that the smaller the amount of serum the less frequent and severe the reactions. Judging from clinical experience, however, there seems to be no constant relation between the incidence of serum disease and the amount of serum injected at one dose or the total amount used in the treatment of a patient. The symptoms usually appear from the 7th to the 10th day after the first dose of serum, although they may appear earlier or later than this. The commonest symptom to appear is an urticarial or erythematous rash and with its appearance there may be an initial rise in temperature. In many cases joints become red, swollen and tender and even an effusion into the joint may take place. There are muscular pains especially in the back. Edema of the face and tongue and of the penis and the scrotum may develop. Inasmuch as the meningeal symptoms are often intensified during serum sickness, care must be taken not to mistake the recrudescence of meningeal symptoms due to a serum disease for a recrudescence of the meningitis. When in doubt as to a differentiation between them, the safest procedure is to make a lumbar puncture and examine the cerebrospinal fluid for meningococci. In many of the patients the symptoms are so mild that treatment is not necessary. In the more severe reactions with itching of the skin, the local application of sodium bicarbonate solution, a 1 per cent menthol solution or calamine lotion often affords relief but sedatives sometimes are required for the itching and it is frequently necessary to give them for the pain which accompanies arthritis. The hypodermic administration of adrenalin in full doses often will cause the edema and urticaria rapidly to disappear.

ANAPHYLAXIS

Although a primary injection of serum does not always sensitize an individual, symptoms of anaphylaxis do occur in about 75 per cent of the patients if they receive serum at such intervals that a week or more elapses between doses. The symptoms may be as mild as those occurring in serum sickness, or they be very severe and alarming. There may be an universal urticaria or a marked edema especially of the mouth, ears, eyes and larynx. The patient may become cyanosed with great respiratory distress. The temperature is often elevated. As a rule the symptoms gradually subside but marked prostration is apt to continue for several days. The severe reactions may occur after a short latent period of time or they may come on immediately (Goodall). Fatal results following the injection of serum are rare. Most of the cases reported have been in individuals who were hypersensitive to protein such as those who have suffered from asthma or in people with the habitus known as status thymico-lymphaticus. In such patients a death almost always occurs immediately following the first injection of serum.

A patient who is sensitive to foreign protein or who has shown symptoms of anaphylaxis at a preceding injection should always be desensitized before the reactivating therapeutic dose is administered. This may be done by diluting 5 cc. of serum with 50 cc. of normal saline solution and injecting intravenously small amounts (1 to 25 cc. of the dilution) slowly at intervals over a period of fifteen minutes. Fifteen minutes after the last injection the full dose may safely be administered. At any time during the administration of serum, if symptoms of anaphylaxis appear, the injection should be discontinued. The attempt may be repeated later after desensitization. The alarming symptoms are combated by epinephrin 1:1000 solution, 5 to 20 minims and atropin grains $\frac{1}{50}$ to $\frac{1}{150}$ injected intramuscularly or intravenously. Whenever serum is being administered these solutions should be ready for immediate use in case symptoms of anaphylaxis develop.

INFLUENCE OF SERUM THERAPY ON THE DISEASE

Statistics which show the effect of the serum treatment of meningitis in comparison with the results of preserum treatment are striking.

Jochmann in 1906 had a death rate of 27 per cent as compared with 53 per cent in the untreated cases; Kolle and Wassermann in 1907 reported a mortality of 47.3 per cent in serum treated cases. Levy had a mortality of 16.2 per cent and 21.7 per cent in two epidemics and Flexner and Jobling reported a mortality of 25 per cent in 393 cases. When it is remembered that the average mortality of meningococcus meningitis untreated by serum was from 60 to 80 per cent whereas the average mortality for three years following serum therapy was 36 per cent, the benefits from the serum can readily be appreciated. The following table of statistics compiled by various observers illustrates the mortality rate before serum treatment compared with that following its use. These figures leave no doubt as to the effectiveness of this form of treatment.

AUTHOR	CASES TREATED WITH SERUM	SERUM USED	SERUM TREATED MORTALITY	CASES NOT TREATED WITH SERUM MORTALITY
Flexner	1300	Flexner's	30.9	70
Netter	100	Flexner's	28.0	49
Robb	300	Flexner's	30.0	72
Dopter	402	Dopter's	16.4	65
Levy	165	Kolle-Wassermann	18.4	52
Steiner	2280	Flexner's	37.0	77

So far as the benefits of serum treatment are shown, one need not look further than the figures which are given above.

The beneficial results of the serum are particularly apparent in the results obtained with small infants. Children under two years of age without serum almost always died and the mortality in those under a year was nearly 100 per cent. While meningitis is still most fatal in young children, a considerable number of infants may be saved, even some as young as three months of age. Seventy-eight patients under two years of age with meningococcus meningitis have been treated in this clinic and the mortality has been 52 per cent. Furthermore with serum treatment the number of complications and sequelae has been greatly lessened as has been pointed out.

The mortality even with serum therapy is likely to vary greatly in different epidemics and at different times in the same epidemic.

Early in epidemics there are a larger number of fulminating cases than at the close and the virulence of the infection tends to subside and to be least in sporadic cases. For these reasons the mortality even with serum treatment is apt to be high at the beginning of the epidemics. The duration of the disease before treatment is begun has a great influence upon the mortality. This has been the experience of all observers as shown in the following chart:

Mortality per cent compared with day of beginning therapy

DAY	FLEXNER	NETTER	DOPTER	CHRISTMANOS	LEVY	FLACK
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Before 3	18	7	8	13	13	9
From 4 to 7	27	11	14	25	29	
After 7	36	23	24	47	28	50

Finally the factor which has the greatest influence on the mortality of meningococcus meningitis is the potency of the serum employed. During 1914 to 1915 when meningococcus meningitis appeared among the armed forces of Great Britain, the results of serum treatment were so unsatisfactory that a number of workers were inclined to believe that as much benefit was obtained from lumbar puncture alone as by the use of serum. Foster and Gaskell in their monograph on cerebrospinal fever not only advocate lumbar puncture as the only reliable therapeutic procedure but suggest that the injection of serum may even do harm. Many of the cases were not treated sufficiently early and the dosage of the serum and frequency with which it was administered varied within wide limits. It was then shown that the quality of the serum was of low standard and its potency practically nil owing to the fact that the strains of meningococci causing the infection were not used in the preparation of the serum. Later when a serum was employed which contained all the types of the organism criticism of the effectiveness of antimeningococcus serum ceased. In the first year of the war the mortality in serum treated cases was 61 per cent. In the following years when a properly prepared and standardized serum was used, it was about 27 per cent. This experience has demonstrated that the commercial manufacturer cannot be permitted to determine the method of preparation and choose his own standard of potency.

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ERRATA

The editors of MEDICINE regret very much that the following errors appeared in the article entitled "The Specific Dynamic Action of Various Food Factors" by Dr. Graham Lusk, in MEDICINE, Volume I, No. 2.

Page 313, line 6: *Read* 24 *for* 14.

Page 316, line 16: (36 a) delete.

Page 318, line 5: *Read* in the first instance was deposited.

Page 318, line 25: *Read* Magnus-Levy.

Page 325, line 6, paragraph 5: *Read* must have affinities *for* must be affinities.

Page 325, last line: *Read* molecules *for* molecule.

Page 327, table, line 1, column 3: *Read* 24.98 *for* 24.81.

Page 333, line 1: *Read* When glucose.

Page 334, line 1, paragraph 4: *Read* oxidations *for* oxidation.

Page 336, line 21: *Read* less *for* more.

Page 339, legend of chart III: Should be one sentence in small caps.

Page 341, paragraph 3: *Read* whereas *for* whereas, as.

Page 342, line 17: *Read* who showed that *for* and showed that.

Page 343, table, line 5: *Read* 30 (calories per hour) *for* 70 (calories per hour).

Page 343, foot of page: *Read* COOH *for* $COOH_2$. Delete bond between formulae of serin and acetic acid.

Page 344, line 8: *Read* Jonas *for* Jones.

Page 345, line 6: *Read* See page 315.

Page 345, paragraph 4: *Read* HOOC- *for* HOO-C.

Page 347, line 13: *Read* glycollic acid *for* glycocoll acid.

Page 350, line 16: *Read* See page 342.

THE ETIOLOGY AND EPIDEMIOLOGY OF INFLUENZA

HANS ZINSSER

New York

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INTRODUCTION

The etiological and epidemiological problems of no disease can be intelligently discussed until we can precede discussion with a clear cut definition of the disease itself. In infectious diseases like smallpox, scarlet fever, measles, diphtheria, and pneumonia, investigation is sure to deal with a material which is amenable to reliable selection on clinical grounds. In the case of influenza it is the difficulty of sharply defining the disease, which has been, and still is, at the bottom of the confusion prevailing in research. Whenever widespread epidemics

of so-called "catarrhal fever" have swept over large sections of the world, the epidemic characteristics in themselves, as well as a certain regularity of onset, sequence and similarity of course, have sufficiently indicated the basic identity of the cases. It has been clearly recognized, however, that except at the very beginnings of every epidemic, clinical manifestations have been dominated by the complications, rather than by the original infection. And these complications, in their localizations, pathology and bacteriology have been subject to wide variations. For these reasons the diagnosis of influenza made upon isolated cases of respiratory infection at times when no epidemic prevailed, has been admittedly more a clinical surmise than a scientifically formulated conclusion. This has been clear to well trained physicians for many years, and the term "influenza" has been used by them during interepidemic periods as a term of clinical convenience, to characterize conditions ranging in seriousness from severe coryza, with systemic symptoms, to fatal lobular pneumonia. It may well be that many of these cases have had a specific influenzal basis, and represent the smouldering embers from which the flames of new epidemics are lighted, but there is no way at the present time of being sure of this in individual cases.

It would be a relatively simple matter if we could base the diagnosis of true influenza upon the isolation of Pfeiffer bacilli, just as we determine the diagnosis of diphtheria by the isolation of the Klebbs-Loeffler bacillus. But for reasons which will become clear presently, this cannot be done. For, even through the Pfeiffer bacillus should eventually prove to be the specific etiological factor in influenza, it is still so frequent as a complicating agent in other respiratory infections, or perhaps as a symbiant in the upper air passages of normal individuals, that its mere presence in the secretions of a catarrhally inflamed mucosa, does not characterize the infection etiologically.

The relationship of this bacillus to the disease presents a problem of great complexity and of many uncertainties which will be discussed more extensively below. Before we can proceed to this, however, it will be necessary to specify more precisely just what we believe should be the proper characterization of uncomplicated influenza in a clinical sense. For unless this is clear it will be impossible to determine

whether bacteriological or other etiological investigations have dealt with the disease itself or with one or another of the manifold complications.

HISTORICAL RÉSUMÉ

In the older works many accurate descriptions of uncomplicated influenza are available. Huxham writing of the epidemic which occurred in Plymouth in the first half of the eighteenth century, describes the disease as one of very sudden onset, chilliness and fever, usually lasting about four days, and rarely ending fatally. He mentions catarrhal inflammations of the nose and throat, and the frequent occurrence later in the disease, of a cough, but lays stress not upon these catarrhal symptoms, but rather upon the suddenness of onset, the fever, the short duration and the low mortality. Arbuthnot in 1732 speaks of a remarkable uniformity of symptoms, "a small rigor or chilliness, succeeded with fever of a duration seldom above three days." He says, "this disease was not in itself mortal, but it swept away a great many of poor, old and consumptive people." Thompson in his Annals of Influenza (London, 1852) summarizes the clinical manifestations by laying stress upon the sudden feverish onset, chilliness, and pains in the neck, back and loins, suffusion of the eyes; coryza and bronchitis are mentioned as later developments. Most of these writers, more especially Thompson, recognized the inflammations of the bronchi, pleura, and lungs as probable complications frequently present, but not as uniformly characteristic as the fever, pains, and the prostration which was often extreme without sufficient apparent reason in any discoverable lesions. It is interesting to note that these early writers described an intestinal form. Thompson speaks of it as follows: "When the lungs are not materially affected, the force of the morbid influence is in some instances directed to the bowels, producing pain and tenderness of the abdomen, and diarrhea, with mucous or dysenteric evacuations."

Leichtenstern described "typical influenza" as follows (we translate literally):

> Typical influenza consists in a sudden fever which is initiated by a chill or frequent chilly sensations, and lasts from one to several days, is associated with severe headache, especially in the frontal regions, vertigo, pain in the

back and legs, disproportionately severe prostration, and loss of appetite. After ten to twelve hours perspiration ensues, and in twenty-four to forty-eight hours the fever has usually subsided in many of the patients, leaving them with great weakness and with pains in the muscles and joints which disappear within a few days.

In almost all of the patients in whom the onset is violent there is an immediately apparent diminution of urine. Many of the sick may not void more than 200 to 300 cc. of urine in twenty-four to thirty-six hours, and with this there is often constipation. Many may show an enlargement of the spleen.

By the third or fourth day as the patients recover, the constipation is relieved, the urine becomes more plentiful, the albumin disappears, and the splenic enlargement recedes.

This is the classical picture of influenza as Leichtenstern sets it down in the summarizing paragraphs at the beginning of his clinical chapter. He adds that: "symptoms of catarrhal inflammations of the respiratory passages and especially of the nasopharynx often supervene upon the manifestations described above, an occurrence which is perfectly natural in view of the localization of the influenza bacilli." Although, therefore, he does not make the direct statement, he implies that he considers the catarrhal inflammations as probably incidental.

It is a singular fact that, in spite of these and other accurate descriptions of uncomplicated influenza, published since the time of Sydenham, the disease has usually escaped general recognition in epidemics until complications have become frequent.

Thus, Heyfelder, who observed the beginnings of the 1889 epidemic in Russia and the East writes of "Sibirisches Fieber," which was at first looked upon as malaria owing to the apparently complete absence of the complicating lesions habitually associated in our minds with influenza. Of particular interest is his statement: "Auch fehlten bei den meisten die Katarrhalischen Affektionen der Respirations-Organen." When the disease appeared in Petrograd, in November, Heyfelder found that it corresponded accurately to the descriptions of an epidemic of "Dengue fever" which was said to have been prevalent in Constantinople during the preceding September.

The recent pandemic furnishes many similar examples of early confusion. When the disease first appeared at Camp Oglethorpe,

Georgia, in March 1918, its precise nature was long undetermined though its similarity to influenza was recognized. Vaughan and Palmer writing of this outbreak say; "The identity of the disease has not been positively determined after nearly a month of observation;" and again they speak of it "as a disease with a strong resemblance to influenza." In Italy Sampietro suggested Sandfly fever, a thought which seems to have occurred to a number of British writers, and which led us, as well, to make a brief study of prevailing insects upon our first contact with the epidemic at Chaumont in May, 1918. Wherever the disease was first seen during the spring and summer of 1918 it was characterized by explosive suddenness of onset, and an enormous morbidity in individual groups within a few days; but it was mild in nature, with little or no mortality, rare complications and so few of the catarrhal symptoms usually associated with clinical conceptions of influenza that those that did occur were not always regarded as characteristic manifestations of the "new disease."

Many of the earlier reports received in the spring of 1918, therefore, were unanimous in agreement with the typical description of Leichtenstern. These made later in the year began progressively to emphasize the greater frequency of mild or severe inflammatory processes in the upper air passages. Fortunately placed observers could follow with considerable clearness the gradual transformation of the clinical types encountered in successive outbreaks, from the mild "three-day fever" of early spring to the grave respiratory illness of autumn. But there was still in the minds of a considerable number of people some question as to the basic identity of the early mild cases, and the severe epidemic bronchopneumonias of October and November.

CLINICAL COURSE OF INFLUENZA

It will be useful to discuss briefly the early cases as we saw them during the Chaumont epidemic, not because the observations made there add much that is new from a clinical point of view, but because they will remove any possible ambiguity concerning our conception of influenza in its pure uncomplicated form.

As far as we can judge, the little outbreak at headquarters was typical of the first advent of epidemic influenza in many places. The population of the town, at the time, consisted of a large office per-

sonnel attached to the military administration, scattered as to billets and places of work; of military units living in barracks and eating at common masses; and of the townspeople. The epidemic descended upon individual military units with the suddenness of a storm, striking a considerable percentage of the men, perhaps most of the susceptible material, within less than a week, and ending almost as abruptly, with only a few isolated cases trailing behind. Among the more scattered office workers and among the townspeople it was disseminated more gradually and trailed along for a longer period.

These early cases were clinically so uniform that a diagnosis could be made from the history alone. The onset was almost uniformally abrupt. Typical cases would become ill suddenly during the night or at a given hour in the day. A patient who had been perfectly well on going to bed, would suddenly awake with a severe headache, chilliness, malaise and fever. Others would arise feeling perfectly well in the morning, and at some time during the day would become aware of headache and pains in the somatic muscles. Occasionally there was nausea. A few of the patients could state the exact hour at which they were taken ill. One of them became suddenly ill at the moment at which he was stepping into line for inspection. Another was taken ill while standing guard, and again another while being shaved. There were of course some cases in which the onset was more gradual, but our personal impression is that the sudden onset was the characteristic one, the more gradual one, the less usual or modified.

The typical course of these cases may be exemplified by that of J. T. W., a draftsman attached to the 29th Engineers. He was perfectly well until May 20, working regularly, his bowels and appetite normal, considering himself healthy. On May 21, at 4:30 a.m. he awoke with a severe headache. He arose, forced himself to eat breakfast and tried to go to work. He began to feel feverish and chilly. At the same time his headache became worse, with pains in the back, and burning in the eye balls. At 2 p.m. he reported sick, and was taken to the hospital with a temperature of 102.8°. At midnight his temperature dropped to 101.6°, and came down to normal by noon of May 22. As he recovered he developed a slight sore

throat, great soreness of the legs and a very slight cough. He recovered completely within a few days.

These cases with a few exceptions developed no rashes. One or two of them had blotchy red eruptions which we felt incompetent to characterize dermatologically. The leucocyte counts ranged from 5000 to 9000. A very few went above this. Sometimes there was a relative increase of lymphocytes, but this was by no means regular. The few spinal fluids that were examined were normal. As to en-

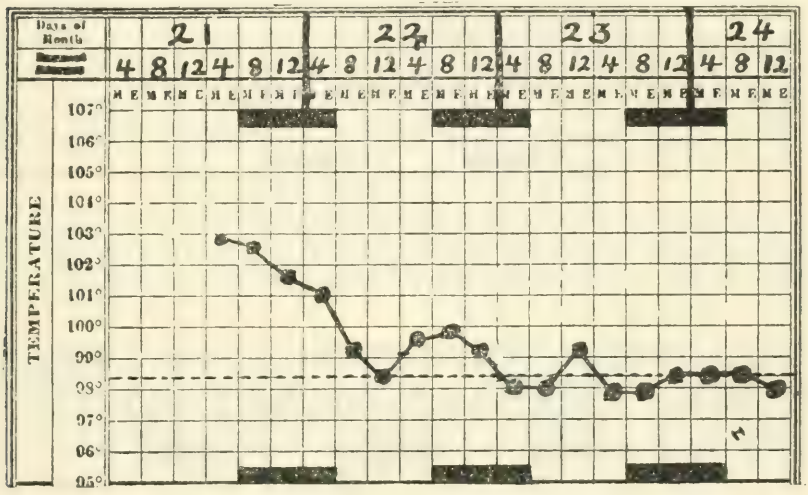

FIG. 1. J. T. W. COMPANY H., 29TH ENGINEERS[1]

Draughtsman. Perfectly well Monday, May 20. Woke up Tuesday, 4:30 a.m. with violent headache. Got up and ate a little breakfast and went to work, then began to feel feverish and chilly. Pain in back and headache and pain in eyes (burning), slight cough and pain in legs. Reported sick 2:00 p.m. Since arrival in hospital cough worse and slight sore throat.

largement of the spleen, we can say nothing definitely. Although we looked for spleens and failed to find enlargements, we are not willing, in view of our limited clinical habits, to say that they could not have been felt by more experienced men.

[1] These charts are taken from the report of Major Hans Zinsser, to the Chief Surgeon, A. E. F., May 31, 1918. Blocked spaces indicate night periods in this and following charts.

We add a few typical charts.

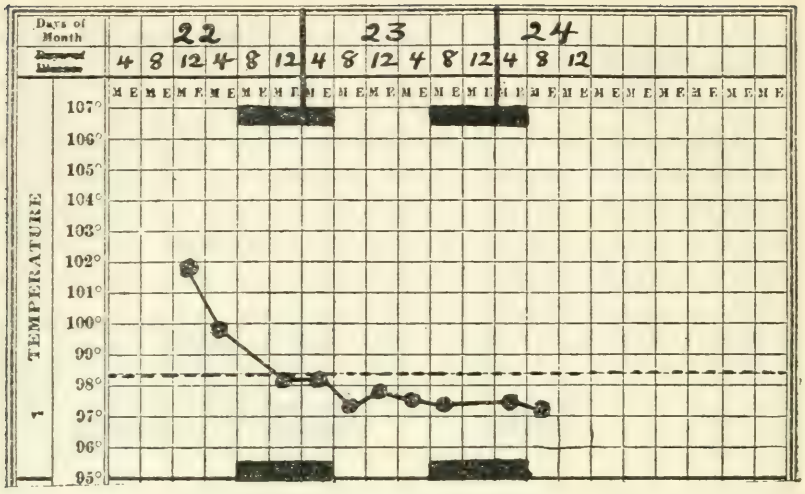

FIG. 2. H. W. COMPANY H., 29TH ENGINEERS

Slept in bunk next to W. Draughtsman, same office as W. Got sick on day after W. On Tuesday, May 21, afternoon, headache, pain in bones, fever, burning in eyes. Did not report sick until Wednesday, May 22. Slight sore throat. Felt better all over before he came to hospital.

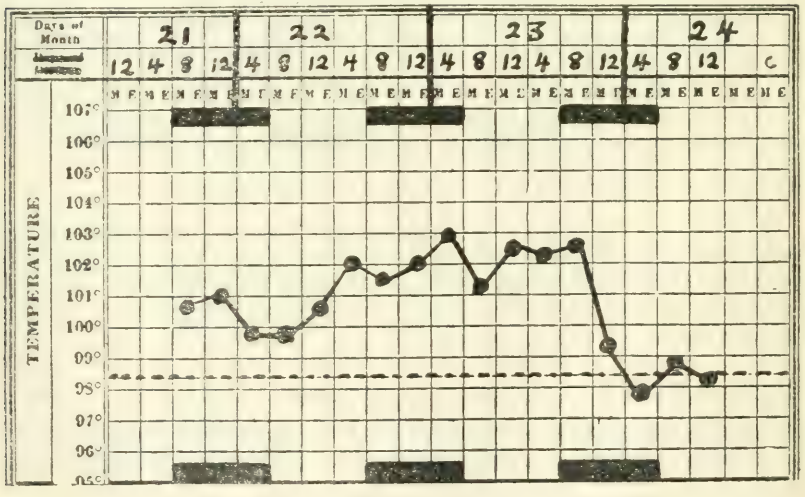

FIG. 3. S. L. COMPANY C., HQ. BN.

Was living with Company D when taken sick. Company Clerk. No one near him sick in same way. Messed with Company D. Felt well Monday, May 20. Tuesday, a.m. felt well until after breakfast, then headache. In afternoon went to dispensary and was sent to hospital. Very slight cough since arrival in hospital. Throat not sore now, and no pains. Is feeling well.

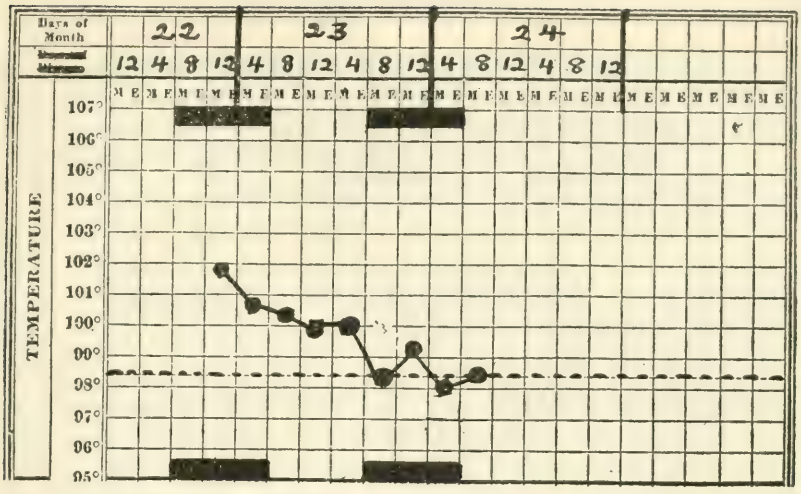

FIG. 4. C. S. COMPANY H., 29TH ENGINEERS

Orderly. Slept 4 bunks from F., sick in hospital now. Began to feel sick while at drill on Wednesday, a.m., May 22. Dizziness, stiffness in muscles, no sore throat. No other symptoms, went to dispensary because he felt feverish. Slight cough since arrival in hospital. Feeling well now.

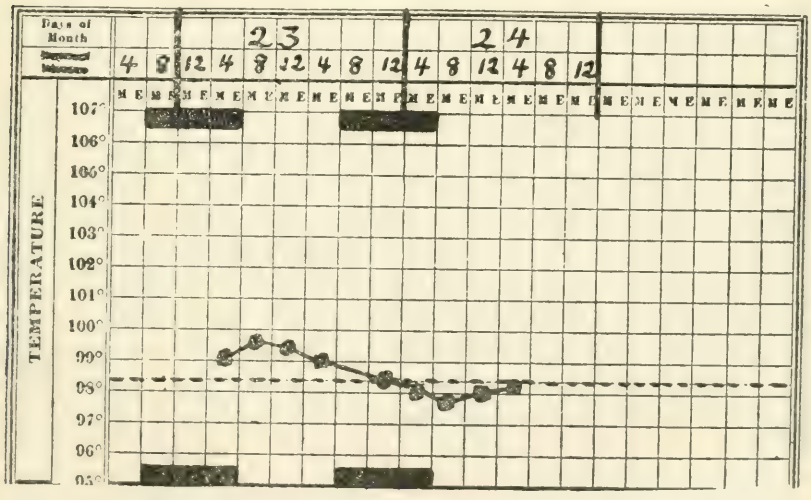

FIG. 5. M. MARINES

Slept in tent with one man, C., who had just come back from hospital. C. returned Monday, May 20. M. began to feel sick Wednesday, May 22, at night. Dizziness and headache, weakness, pain in back and legs. No nausea, nothing referable to intestines.

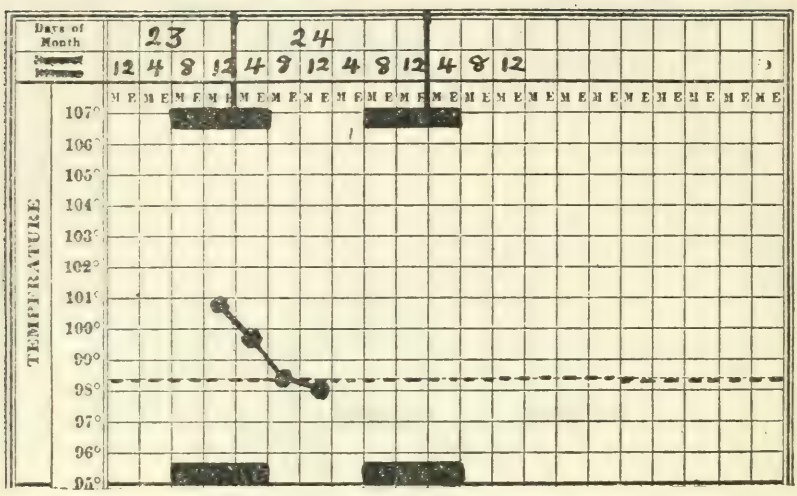

FIG. 6. R. S., A. M. T., COMPANY 304

Cook. Worked all day Wednesday. Began to feel sick about 4:00 p. m. Headache after supper, nausea. Not very sick, sent to hospital by attendant at dispensary.

Soon after this we observed the disease in a division, the 42nd, then holding a part of the line in front of Baccarat. Here it had already developed a somewhat different nature, due, we believe, to the fact that the men of this division were not, as were those at Chaumont, living in a rest area, but were actively engaged in military operations, working, sleeping, and eating under conditions that involved greater fatigue, less protection against weather, and greater crowding in sleeping quarters. The Baccarat cases were much more frequently catarrhal; sore throats, coughs and more serious respiratory complications were more common. However, they were usually coupled unmistakably with an underlying typical influenzal attack, sudden onset, pains and short lived fever. Moreover, there were a great many of the entirely uncomplicated cases interspersed with the others.

Still later, in September, October and November, respiratory complications were so frequent and severe, came on so early in the disease, and the pneumonia mortality became so high that the fundamental identity of these later cases with the early three-day fever might easily have been lost sight of by observers who had not followed the gradual transformation.

In consideration of these facts, it is apparent that etiological or other investigations can throw no light upon the problems of influenza unless they are carried out with a clear understanding of the differentiation between the complications and the basic disease.

The serious respiratory infections of the bronchi and lungs we can set down with reasonable certainty as complications due, certainly in the overwhelming majority of cases, to secondary bacterial invaders. It is a matter of considerable difficulty, however, to know exactly where the basic disease stops and the complications begin; and whether we must regard the mild sore throat and conjunctival infection which so often accompany the simple cases as a part of this basic clinical picture, or as the simplest variety of complication. This is much more than an academic question, since, as we shall see, the bacteriological analyses of such lesions have played an important rôle in etiological investigations.

ETIOLOGY OF INFLUENZA

Former epidemics

The significance of sharp clinical definitions for etiological research in influenza is obvious. The simple form of the uncomplicated disease is common only during the early stages of epidemics. After this, most of the cases may perhaps begin with this basic condition, but are very rapidly complicated by more or less serious inflammatory involvement of the respiratory passages. Some of the milder and perhaps some of the more serious and even fatal of these complications may be due to the infectious agent which causes the original disease; but a great many of them we know are caused by secondary invaders, and for this reason bacteriological analyses made from the secretions and the lesions of the respiratory passages in such cases must be interpreted with constant realization of the possibility that we are dealing with secondary invaders and not with the primary infectious agent. This has been the difficulty in etiological influenza research, and in the light of this confusing state of affairs, no results are of great value unless combined with a correspondingly careful clinical analysis of the cases from which the material has been taken.

When the pandemic of 1889 was beginning to trail into its last stages

there seemed to be little doubt in the minds of investigators concerning the etiological significance of the Pfeiffer bacillus. At the present time, with the experiences of another outbreak behind us, we are less certain of this relationship than we were before.

It will be well to state, at the beginning, that we do not believe that final conclusions concerning the etiology of influenza are warranted at the present time. The problem has been a singularly difficult one, largely owing to the indefinite clinical conceptions of the disease alluded to above. For these reasons one cannot do justice to the etiological problem without discussing at some length the more important investigations which have dealt with this subject during the two last epidemics and in the interepidemic period.

After 1889 many etiological "suggestions" (we had best term them) were made, prior to the publication of Pfeiffer's observations. Klebs reported that he had found protozoa in influenza lesions, a claim which finds an interesting parallel in the recent reports of Binder and Prell who have described minute coccoid bodies in the tissue spaces around blood vessels in influenza lungs, and the subsequent development in cultures from such material of small organisms which they regard as "chlamydozoa." Comment on such findings is unprofitable at the present time. We can merely "file" them in our minds for reference and, perhaps, future explanation. The past has been too rich in misleading interpretations of so-called "chlamydozoan" cell inclusions (variola, trachoma, etc.) to encourage optimism concerning such claims.

As in the recent outbreak the preceding one was the occasion for etiological proposals involving the Gram-positive cocci, more particularly the pneumococcus and streptococcus groups. However, it is perfectly natural that bacteria which habitually inhabit the upper respiratory passages, and are potentially pathogenic, should be isolated with great frequency from influenza cases, and, therefore, incite suspicion of etiological importance; but none of these can be seriously considered. Indeed, in the light of our present differentiation between the basic disease and the complications, the streptococci and pneumococci may be regarded as practically eliminated as primary causations of influenza. The same is true to an even greater degree of organisms like micrococcus catarrhalis, meningococcus, para-

typhoid bacilli, and many other bacteria which have been isolated from time to time as characteristic findings in small groups of cases occurring in special localities. Some of these investigations will be briefly dealt with in a later paragraph.

We believe, indeed, that we are justified in basing our discussion of etiology upon the assumption that none of the bacteria so far described can be seriously considered in this connection except the group of haemophile organisms of which we speak as "Pfeiffer bacilli." If influenza is truly a disease of bacterial causation these precede all other bacteria in etiological likelihood.

Pfeiffer published his first announcement in 1892, reporting that he had found the organisms, which are now familiar to us as the typical influenza bacillus, in the sputum of patients, but had failed to find them in normal controls. In a subsequent article in the Zeitschrift für Hygiene (13, 1892) he brought together the large material of his researches, the results of which may be stated briefly as follows.

The organisms were present in large numbers in the sputa of early cases and, at this early stage, were largely extracellular. Later, most of the sputum organisms became intracellular and, in the milder cases, gradually disappeared. In cases with pulmonary complications which came to autopsy, if the bacterial contents of the respiratory passages were examined in progressively downward stages from the pharynx into the lungs, influenza bacilli were found with increasing predominance as the examination proceeded toward the smaller bronchi and bronchioles. In the pulmonary tissues themselves they were sometimes present in pure culture. (Compare with observations of Richard Taylor, 1918. Vide infra.) He cultivated the bacilli on haemoglobin media and described definite cultural and morphological characteristics.

The great importance of Pfeiffer's announcement naturally led to extensive work on the isolation of haemophile bacilli all over the world. The results seemed to indicate rapid and complete confirmation of his claims. Weichselbaum found the bacilli in the lungs of a considerable number of autopsies on cases that had died of bronchopneumonia secondary to typical influenza. Huber, Baümler, Kretz, Chiari found them in sputum, lungs and nasopharyngeal cavities of many typical cases. Kruse found them in 100 per cent of the early

cases he examined. With increasing frequency the organisms were isolated not only from the respiratory passages, but from other organs in which lesions secondary to influenza had developed. Pfühl found them in the spinal fluids of soldiers that had died of meningitis, complicating influenza, and Nauwerck found them in sections of the brain in a similar cases of encephalitis. It would be possible to multiply indefinitely the accounts of similar findings. Careful investigations during these years seemed to yield positive results with such regularity that isolation of the bacillus was utilized diagnostically, and very little or no doubt concerning its etiological significance remained at the end of this epidemic. A few such accidents, moreover, as that of Kretz who infected himself from a pure culture and came down with an acute respiratory catarrh and many of the symptoms of a typical influenzal attack, appeared to remove all remaining uncertainty. Pfeiffer's original claims seemed to have been satisfactorily confirmed, and his own conclusions were accepted by most of his contemporaries.

The term "influenza" which had hitherto represented a purely clinical conception was now changed to an etiological one, and its diagnostic use was governed largely by isolation or failure to isolate influenza bacilli. This conception was further strengthened by studies such as those of Tedesco and of Scheller who found that, during the years following the epidemic period, the isolation of influenza bacilli from respiratory lesions became more and more infrequent as the epidemic receded into the past. At the same time fewer and fewer carriers of the organism were found among normal individuals. Even in patients who appeared to present the clinical picture of so-called "grippe" the bacilli became more and more rare in the course of successive years. Leichtenstern states that, in 1892, toward the end of the epidemic, a very large number of pure influenza bacillus infections of the bronchial tree occurred all over Germany, but that, in 1900, Wassermann had the greatest difficulty in finding influenza bacilli at all, even in cases clinically diagnosed as Influenza in Berlin. A similar statement in regard to work done in 1903 was made by Beck; and, indeed, most bacteriologists will probably confirm our own experience to the effect that, during the years immediately preceding the war, the discovery of influenza bacilli in the respiratory passages

of adults, was not particularly frequent. And when it did occur the clinical condition was rarely one which could properly be spoken of as influenza.

Thus, the frequent association of the organisms with typical cases both in complicating and secondary lesions, their presence in a considerable number of normal individuals during times of epidemic prevalence and the progressively diminishing frequency of such findings in the course of the years following the epidemic, all these observations seemed to indicate clearly that the bacilli were etiologically related to the disease.

Nevertheless, during subsequent years evidence accumulated to show that even in the interepidemic period the Pfeiffer bacillus group was present in a variety of human lesions, sometimes as a harmless saprophyte, sometimes with definite pathogenic properties, and many times in conditions which had little or no resemblance to clinical epidemic influenza. It appears that after the epidemic had subsided the organism was still widely distributed among human beings, and a study of this interepidemic distribution is necessary in order that we may possess a complete picture of the pathogenic possibilities of bacteria of this group. For if we should find that these organisms can exist either as harmless saprophytes or as pathogenic agents never giving rise to typical influenza in these periods of interval, this would detract considerably from the trustworthiness of any conclusions formulated in regard to their specific pathogenic properties.

Leichtenstern has made extensive studies of the literature with the purpose of ascertaining the nature of the lesions with which influenza bacilli were most frequently associated during the years following the pandemic of 1889 to 1892. These and subsequent studies reveal an astonishingly wide distribution of the organisms, and their association with a variety of lesions second only to that of the Gram-positive cocci.

The presence of the bacilli in tuberculous processes was noted by Pfeiffer in his early studies, and since then has been observed by Ortner and many other workers. It is especially frequent when bronchiectatic cavities exist. A series of such cases was reported by Boggs, in which the influenza bacilli were apparently symbiotic with other bacteria in the cavity fluids, without being responsible for symptoms of any considerable severity.

In the blood, at autopsy, influenza bacilli have frequently been found. Jaehle (Zeit. f. Heilkunde, 1901, XXII, 190) isolated the bacilli from the heart's blood in two of 48 scarlet fever autopsies. In 19 of these pulmonary influenza bacillus infection was present. In 23 autopsy blood-cultures of patients dead of measles, he found the influenza bacillus 15 times. In one of these he found the bacilli in the blood when the only other influenza bacillus lesion in the body was a massive infection of the tonsils. He found them 5 times in the blood of 9 cases of chickenpox, and twice in 24 cases of whooping cough. He found them also in the respiratory passages in 15 cases of diphtheria; in one of these the bacillus was present in the blood as well.

Wynekoop in 1903 studied the presence of influenza bacilli in inflammations of the larynx, pharynx and nose. In certain forms of chronic laryngitis he often obtained the organisms in pure culture. He found them in tonsillitis, and described a peculiar form of severe pharyngitis in which they were present with considerable regularity. Some of these cases simulated mild diphtheria. He often obtained the bacilli from the conjunctivae, and emphasized the fact that pure influenza bacillus infections usually tend to rapid recovery.

Madison has collected 30 cases in which influenza bacilli were grown from the blood during life. He himself reported a primary influenza bacillus bronchopneumonia in which smears from the sputum constantly showed large numbers of influenza bacilli, and in which a positive blood culture was obtained. Similar cases have been described by Meunier, Horder, Smith, Slawyk and others.

Infections of the central nervous system with influenza bacilli have been reported by Pfühl; influenza meningitis has been extensively studied by Wollstein, by Dudgeon and Adams, Saathoff and many others. A curious observation of interest in this connection has been related to us by Dr. Emmet Holt, who tells us that although influenza meningitis had not been infrequent in the Baby's Hospital in New York during the interepidemic period, he had seen practically none of these cases during the recent epidemic.

The presence of the organisms in suppurations of the nasal cavities, the orbit and frontal sinuses, has been reported in a great many cases. We have seen several examples of this, some in children, some in

adults, in which a chronic influenza bacillus infection of the nasal cavities and antrum was apparently responsible for intermittent asthmatic attacks; and the persistence with which these organisms may remain chronically present in the deeper respiratory passages of children following bronchopneumonia, bronchitis, or whooping cough, and their apparent responsibility for prolonged cough and general malnutrition are too well known to require comment.

The bacillus has also been occasionally found in acute and chronic gallbladder infections (Heyrowsky and Kuina).

Among the most interesting studies on the association of influenza bacilli with interepidemic pulmonary disease are those made by Wollstein upon children at the Babys' Hospital in New York. In 1906 at a time about midway between the two last pandemics Wollstein published observations on children suffering from various types of respiratory infection. Briefly summarized, her results were as follows: Influenza bacilli were present in 16 of 53 cases of bronchopneumonia, and in 1 of 8 cases of lobar pneumonia, when the cultures were taken during life. Of 13 cases of bronchopneumonia studied at autopsy the organisms were found three times. They were found 6 times in connection with tuberculosis, and in isolated cases in various other conditions in which the lungs were inflamed. In agreement with other workers, she frequently found the organisms in whooping cough, and 9 times in 27 cases of measles. This last result is in keeping with many other investigations upon measles. Liebscher for instance found the organism in 11 of 57 measles cases during life, and 3 times in the lungs at autopsy; he observed a higher death rate in the influenza bacillus cases than in the others. Süsswein saw the bacilli in the nasal secretions in almost 50 per cent of such cases, and 3 times in the lungs at autopsy. Jaehle and Jochmann have made similar observations, and Albrecht and v. Preyss obtained the organisms from the lungs in post-measles pneumonia.

The great frequency of conjunctival infection with the influenza bacillus has been mentioned. It is quite probable (Williams, Wollstein, and others) that the so-called Koch-Weeks bacillus should be regarded as belonging to the group of the true influenza bacilli, and many mild and severe conjunctival inflammations have been found to be due to these organisms. Zur Nedden, Wynekoop, Williams, Woll-

stein, and others have described a great many such cases, and Wyne koop and Wollstein particularly have reported instances in which severe hemorrhagic inflammations of the conjunctivae have shown influenza bacilli in pure culture. In some of these mild systemic symptoms were present.

It is interesting to note, that Wollstein in her extensive studies on influenza bacilli in babies has found the organisms very rarely in the throats of healthy children or in the throats of children who did not have respiratory lesions. She states that whenever the organisms were found, they seemed to exert a definite influence upon the severity of the disease. Death rates were higher, and in the bronchopneumonias with influenza bacilli there was higher temperature, greater prostration, and a longer duration of the illness. Such observations would particularly incline one to accept Ortner's opinion that true influenza may remain endemic in the intervals between epidemics as a definite clinical condition, an opinion confirmed to us on purely clinical grounds by a number of experienced physicians.

Indeed, in the intervals between large influenza epidemics there may be occasional isolated epidemics in closed institutions, such as asylums and homes for the aged. Such epidemics were reported by Sturrock in 1900, and by Nobecourt and Paisseau in 1905. Unfortunately etiological investigations of such outbreaks have yielded little additional light.

Carriers

That the carrier state may persist after infection with influenza bacilli is unquestionable. During the last epidemic Pritchett and Stillman cultivated the influenza bacillus from the mouths of 93 per cent of cases of influenza and bronchopneumonia, and at the same time they found it in 43 per cent of normal individuals. Lord, Scott and Nye during the same epidemic found influenza bacilli in 76 per cent of 34 men in the Harvard Students' Training Corps. At Camp Funston, Opie, Freeman, Blake, Small and Rivers found influenza bacilli in the mouths of 35.1 per cent of healthy soldiers. Subsequently, Winchell and Stillman found that the percentage of influenza bacilli in the throats of normal people during post-epidemic periods was as high as it was during more active epidemic stages. In 150

individuals they found the organisms in 41 per cent. In a boys' orphan asylum in which no influenza had occurred during the epidemic, 39 per cent of the throats were positive, a percentage which was equal to that found in convalescents in an institution in which about half of the inmates had had the disease. They found carriers who had retained the organisms for four and five months after convalescence.

The experiments of Bloomfield have to a certain extent contradicated this in that Bloomfield introduced three different strains of the bacilli in large quantities into the upper air passages of normal individuals without being able to produce the carrier state. He obtained neither local nor general pathological results, and the organisms rapidly disappeared. We will recur to this work of Bloomfield below. He draws the conclusion that we can tell very little about the persistence of influenza bacilli in the throats until we know more about the subclassifications of these organisms, since he sometimes isolated, from the inoculated individuals, strains which differed in serological grouping from the strains which he had introduced. Kretz, on the other hand, found influenza bacilli in the throats of patients months after their attacks, and Rosenthal has isolated the organisms from the larynx and the trachea in about 15 per cent of the cases he examined. Davis's studies have shown the organism in 10 per cent of normal people. Klopstock found influenza bacilli in 5.1 per cent of 1000 routine sputum examinations made at a Berlin hospital, and Wohlwill has made similar observations.

We may summarize, therefore, our knowledge of the influenza bacillus up to the time of the last epidemic somewhat as follows:

During the epidemic of 1889 influenza bacilli were found in a large percentage of the cases examined, often in pure culture and in all parts of the respiratory passages. They were found in pure culture particularly in early cases, but as the epidemic trailed towards its endings and severe complications were more common, fewer and fewer pure cultivations were obtained. At this stage of the epidemic the organisms were still the predominating ones in most of the cases, but were now almost always found admixed with pneumococci, streptococci and other bacteria. They were present also in a great many of the complications which occurred in parts of the body, other than the

respiratory tract. During the last stages of the epidemic and during the years immediately following, there seems to have been a gradual diminution of frequency of influenza bacillus findings in respiratory diseases, even in those which clinically resembled the complicated epidemic cases.

When finally it seemed that epidemic influenza had completely disappeared it was found that bacilli of the hemophile group had become established as common inhabitants of the respiratory passages of man, sometimes playing the rôle of harmless symbiants, sometimes definitely associated with pathological processes. They have been found associated with suppurations of the cavities of the head, various forms of conjunctivitis, and with a variety of other diseases. A curious development is that in pulmonary complications of conditions not primarily caused by them, they have been found with considerable regularity. Thus, they are now recognized as almost universally present in the later lesions of whooping cough and as commonly present in the pulmonary complications of measles, less commonly in scarlet fever and diphtheria. In such cases especially when they occur in children, they seem to be distinctly pathogenic, either independently causing lobular forms of pneumonia, or else as shown by Wollstein, contributing definitely to the severity of the disease.

It has also been found that the carrier state can exist at such time, and that the bacilli may be present for long periods in the nasopharyngeal mucous membranes of normal individuals or in bronchiectatic cavities without causing injury either by invasion or by toxemia.

In our final summary we will attempt to coördinate these facts with the results of more recent studies.

Recent epidemic of 1918

When we turn to the bacteriological analyses that have been made during the recent epidemic, we are overwhelmed by the wealth of reported material, but confused at the same time, by its indefiniteness in description of technique and by the frequently defective clinical characterization of the cases studied.

It will be noticed that during the early phases of this epidemic, workers all over the world failed to find influenza bacilli. Thus in

Germany the earliest reports (Kolle of Frankfurt, Friedemann of Berlin, Mandelbaum of Munich, Citron of Berlin, and Bernhardt of Stettin) agree in failure to find influenza bacilli. Coca and Sapata made a similar negative report from Spain. Sampietro in Italy suggested the similarity of the disease to sandfly fever, owing to inconclusive bacteriological reports, and McIntosh, writing in 1918, emphasized the widespread failure to find influenza bacilli throughout the world. He himself made negative examinations on early cases in London in 1918; and similar negative results were noted in a summary in the Medical Supplement to the Daily Review of the Foreign Press brought out by the British Medical Research Committee in October, 1918. Of American workers in France the same thing was true. Indeed, the clinical picture of the cases first observed was such that there seemed to be no focus of localized inflammation from which it would have seemed profitable to take cultures. Our own experience in this respect was similar.

It must be remembered that when the epidemic first appeared, there were many who felt quite uncertain about its nature, and the systematic and purposeful search for influenza bacilli did not generally begin until an increased number of sore throats, upper respiratory catarrhs, etc., began to appear. Soon after the outbreak at Chaumont, the writer saw a similar epidemic in troops that were in the line and in reserve, and in these the presence of respiratory symptoms gave a more definite clue to the importance of cultural work on the nose and throat. In consequence, both the local laboratory officers, Lieutenants Jacobs and Avery and the writer, began to take throat cultures, and influenza bacilli were found in a considerable number of cases. Soon after this, on the writer's return to Dijon on temporary duty, a small epidemic of early uncomplicated cases was reported to Dr. MacNeal who was then the commanding officer of the Headquarter's laboratory, and MacNeal and the writer obtained pharyngeal cultures from 14 of these men during the first 24 to 48 hours of their disease. None of these showed more than a mild reddening of the pharynx with very slight discomfort, and in all of them influenza bacilli were demonstrated either by smear or culture. There can be little doubt of the fact that, at least in part, the failure to find influenza bacilli in the upper respiratory secretions of the early cases must be

attributed to two factors, first, the omission of systematic culture because of failure to recognize the disease as originating in the respiratory organs, and, second, because of inadequate technique on the parts of workers. It seems that technique was universally defective during the early phases of the epidemic, and it was not until media were improved (trypsinized blood agar was introduced in England, and modifications of what we speak of as the "chocolate" broth and agar in America and Germany) that results of reasonable accuracy were obtained. Also, a large number of workers, who had had little experience with the influenza bacillus, rapidly learned to manipulate this organism more skilfully. Following this, as the nature of the disease was recognized, a large number of analyses were made, and influenza bacilli were demonstrated in increasingly higher percentages.

It would be extremely difficult to attempt a complete review of all the bacteriological work done during this epidemic. We have selected from the literature a group of reports which are representative of the best work done in this connection during the epidemic. It has seemed useful to append to such a tabulation a statement, in each instance, of the nature of the cases and the source of the material. (See pages 236–242.)

A cursory survey of these reports shows that in the large majority of carefully investigated cases influenza bacilli were found in a high percentage of the examinations. The organisms have been present in over 70 per cent of most of the carefully studied series, and in a number of instances they have been present in over 90 per cent. Our own small group of early cases, like the series investigated by Schmidt, Deitrich and a few others, have shown the Pfeiffer bacillus in 100 per-cent, and a large majority of the workers who have had occasion to study autopsies as well as sputum and nasopharyngeal material, declare that no other organism was found with comparable regularity. In many instances it was found in pure culture. Thus, Wolbach in 28 carefully studied autopsies, found it 14 times in pure culture. Dick and Murray had similar results, and Lister and Taylor in South Africa as well as Leichtentritt in Austria found it alone in no small number of their cases. Mayer, working in Vienna states that whenever he found the organisms in pure culture, the cases were mild, corresponding more nearly to the uncomplicated disease. He adds

that he thinks that all fatal cases are due to complications, a statement which we believe to be true in general, but to which there are not a few exceptions. An interesting contribution is made by Capt. Richard Taylor, who studied the flora of the respiratory tract, from the pharynx downward toward the lungs, in cases which came to autopsy, a procedure similar to that carried out by Pfeiffer in 1891. He states that influenza bacilli were found rarely in pure culture in the trachea and secondary bronchi. Here they were usually associated with various Gram-positive and Gram-negative cocci. As he proceeded downward toward the alveoli of the lungs the bacilli were more and more free from other organisms; and in the smallest bronchi and bronchioles they were either alone or together with only one form of coccus. In the lungs themselves, however, pneumococci and streptococci predominated, though influenza bacilli were often present. We agree with the comment upon these findings made by MacNeal who takes them to indicate that the infection was primarily due to the influenza bacillus, with secondary invasion advancing along the trelisses of inflammation so produced. Similar observations have been made by Loewenthal in Vienna, and a number of other observers have laid stress upon the fact that influenza bacilli, even in complicated cases, are often found quite low down in the bronchial passages.

It is important to note that blood cultures have rarely been positive. When taken during the very early stages of the disease, or at stages in an epidemic during which the mild three day or four day fever types predominated, blood cultures have almost invariably been sterile. In severe cases occasional positive results have been obtained, but this has been rather the exception than the rule, and the great majority of blood cultures taken on severe and complicated cases of influenza have yielded either streptococci or, more often, pneumococci of one or another type.

The difficulty with most of the etiological investigations has been the inability of the investigators to select and control their material, and for this reason percentage results obtained in many cases may be misleading. The researches from which the most useful information can be obtained are those in which workers have been able to group their cases and control their material, both as to the time of the

WORKER AND REFERENCE	NATURE OF CASES STUDIED	TOTAL NUMBER OF CASES ANALYZED	MATERIAL STUDIED	INFLUENZA BACILLI	REMARKS
				per cent	
Mathews, Lancet, 1918, 2, 695	Early in epidemic broncho-pneumonia	12	Nasopharyngeal mucus	84	Concludes that influenza bacillus most frequently predominating organism. Never got positive blood cultures
Dietrich, Lancet, 1918, 2	Bronchial pneumonia	7	Autopsy material	100	None
Hicks and Gray, Lancet, 1919, 1, 419	Early epidemic cases		Nasopharyngeal swabs and sputum	70 to 80	All of the cases showed pneumococcus with influenza bacillus. Never found the organisms in pleural exudates in which pneumococci and streptococci were present. 50% of the severe cases had pneumococci in blood stream
Rose, Lancet, 1919, 1, 421	Severe cases with bronchopneumonia	24	Smears and cultures from lungs	63	These cases in British Guiana in November 1918
Lister and Taylor Pub. S. Afric. Inst. Med. Res., 1919, i, 212, April 30	Epidemic cases in Transvaal	56	Lungs and autopsy material	91	Usually associated with Gram-positive cocci, but in three cases of broncho-pneumonia, Bacillus influenzae found in pure culture
Leichtentritt Deut. med. Woch., 1918, 1419	Mild and severe	Not stated	Lungs and sputum	51.6	States that he found them in the lungs in pure culture on numerous occasions, and in isolated cases in the spleen and in the brain. Rarely, but on few occasions, found them in the blood

Neufeld and Papamarku, Berl. klin. Woch., 1919, 9. Deut. med. Woch., 1918, 1181			Smears from pharynx and tonsils	Large percentage but actual number not given	
Loewenthal, Berl. klin. Woch., 1918, 1170	Typical influenza cases (early)	85	Droplets coughed against blood plates	24	
Uhlenhuth, Med. Klinik, 1918, xiv, 777	Typical epidemic cases 2 series				At the same time took pharyngeal smears and cultures from 100 people in another region in which no epidemic has as yet occurred and found them all negative. He attributes the contrast between his favorable results and the negative ones of others to his use of Leventhal's medium, corresponding to our chocolate agar
		51	Sputum	25	
			Pharyngeal smears	25	
			First series: Blood cultures, all sterile		
			Second series:		
		47	Sputum	46.8	
			5 blood cultures, all sterile		
Bergmann, Deut. med. Woch. 1918, xliv, 933	Variety of epidemic cases		Bacteriological work intensively done on 10 cases, 70 per cent positive	70	
Jordan, Jour. Inf. Dis., 1919, xxv, 28	Selected typical cases mild and severe		Material from upper respiratory tract	64	States that no single organism was constantly predominating, but that Pfeiffer bacillus is more conspicious than any other organisms and next to the diplococcus found by Mathers, at Camp Mead, pneumococcus 20 per cent of cases and Gram-negative very frequently

WORKER AND REFERENCE	NATURE OF CASES STUDIED	TOTAL NUMBER OF CASES ANALYZED	MATERIAL STUDIED	INFLUENZA BACILLI	REMARKS
				per cent	
Keegan, Jour. Amer. Med. Assoc., 1919, lxxi, 1051	Autopsy material and lung puncture	23	Smears and culture	82.6	In only 4 cases was Bacillus influenzae not found at all, and in these there was a haemolytic streptococcus. In 31.6 per cent of his cases, Bacillus influenzae was present in pure culture
MacNeal and Pease, Report to the chief surgeon, American Expeditionary Forces	Influenzae bacilli found in every case examined				
Weiss, Similar report of the 88th division, October, 1918		35	Sputum	85	
Neal, Similar report, November, 1918, Jonchery			Nasopharyngeal mucous showed influenza bacillus	90	Blood cultures of 5 cases showed pneumococcus II in two of them.
			Pneumococcus type I	2	
			Pneumococcus type II	2	
Neal and Frieberg, Similar report 26th Division, September, 1918			Nasopharyngeal smears 54 per cent positive for influenza bacilli	54	

Holman and coworkers, Army Hospital, Pittsburg, report to the chief surgeon, American Expeditionary Forces	Of 31 cases, 24 were positive for influenza			80	These observers found influenza bacilli remaining in the nasopharynx for a long time after the disease, and consider the carrier state often established. Favorably inclined to the etiological importance of the influenza bacillus
Park, Williams and coworkers, Amer. Public Health Jour., 1919, ix, 45	1 to 200 cases examined during first to sixth day of disease				

GROUP	B. INFLUENZA			GROUP	CONTROLS			MATERIAL	AUTOPSIES		
	Present	Absent	Per cent positive		Present	Absent	Per cent		Present	Absent	Per cent positive
Hospital cases	160	40	80	Nurses, contagious	4	6	40	Lungs	24	6	80
Marines	30	0	100	Nurses, non-contagious	1	7	9	Pure culture	5	25	17
Home for children	47	1	98	Measles	4	2	67	Trachea	26	1	96
				Admission ward	4	5	41	Heart's blood	3	27	10
				Home for girls	2	32	6				
				Preventorium	14	25	33				

Okawara and Tanaka, et al., Kitasato Archives 1919, 2.	Early cases uncomplicated	Nasal secretions, sputum and autopsy material	70	

WORKER AND REFERENCE	NATURE OF CASES STUDIED	TOTAL NUMBER OF CASES ANALYZED	MATERIAL STUDIED	INFLUENZA BACILLI	REMARKS
				per cent	
Eyre and Lowe, Lancet, October 12,1918		14	Sputum	86	None
Schmidt, Munch. med. Woch., 1918, 1415	Typical complicated and uncomplicated grippe	60	Sputum and nasopharyngeal mucous	100	He states that over a year before this, that is 1917, there was an epidemic of influenza on the Eastern Austrian Front and thinks that this may be the origin of the epidemic
Mayer, Wien. klin. Woch., 1919, 82	Typical epidemic cases	210	Nasopharyngeal mucous	30.1	He states that none of the cases died in which influenza bacilli were found in pure culture. That all deaths were due to secondary pneumococcus and streptococcus infections
Gruber and Schudel, Munch. med. Woch., 1918, 905	Pneumonias, etc.	250	Autopsy material	6	These writers in the large majority of cases found Gram-positive diplococci and streptococci which they regard as secondary invaders
Loewenfeld, Wien. klin. Woch., 1918, 1274	Dead of secondary pneumonia	45	Bronchial mucous and lungs	80 in bronchial mucous. Fewer in lungs	Loewenfeld believes it extremely important to take cultures from the bronchial mucous and pus, and states that they are rarely present in the lesions in the lungs themselves
Materna and Penecke, Wien. klin. Woch., 1918, 1221	Fatal pneumonias	27	Lungs	74	Their favorable results they claim were due to great care in the bacteriological methods, to neglect of which they attribute failures of others

Loewenthal, Berl. klin. Woch., 1918, 1170	Early cases	85	Patient's coughed upon blood plates	23	
Dick and Murray, Jour. Inf. Dis., 1918, xxv, 6	Variety of typical cases	150	Direct smears and cultures	63.2	Describes a great variation in size of the influenza bacilli in the sputum smears, and often cultivated in pure culture. Some times present in enormous numbers, and many within the leucocytes
Hamberger, Meeting Med. Inst. Chicago, Feb. 21, 1919	Cases from Camp Taylor		5 cases of pneumonia at autopsy showed pure Pfeiffer bacillus		10 cases at autopsy during 4th week of epidemic showed no influenza bacilli, but pure pneumococcus
Wolbach, Bull. Johns Hopkins Hosp., April, 1919, xxx, 104	Autopsy material at Camp Devens	28		82	Of 23 cases, he found the influenza bacillus in pure culture in 9. Of 28 cases by culture and histological methods he found B. I. in 23, and in 14 of these in pure culture. It was in pure culture in some of the later cases. In some cases in which these organisms were not in the lungs, he found them in cultures from the nasopharynx or from the middle ear. Influenza bacillus occurred with more constancy than any other organism, others being usually Gram-positive cocci
Chesney, Report to the chief surgeon, American Expeditionary Forces, 1918	Cases at Valdehan		Material from respiratory tract	Clinical cases, 46.2 positive; Contact cases, 41.6 positive; Non-contact cases, 7.1 positive	

WORKER AND REFERENCE	NATURE OF CASES STUDIED	TOTAL NUMBER OF CASES ANALYZED	MATERIAL STUDIED	INFLUENZA BACILLI	REMARKS
				per cent	
Taylor, Kenneth. Similar report to the chief surgeon	Various respiratory cases during epidemic	35	Material from respiratory tract	46	46 per cent bacillus influenzae 74 per cent pneumococcus 51 per cent streptococcus hemolyticus 87 per cent sputum bronchial pneumonia 87 per cent pneumococcus 33 per cent streptococcus

disease at which it was obtained, and in the manner of taking. Among the most satisfactory researches in this respect are those of Park, Williams and collaborators from the New York Department of Health Laboratories. These investigators with an extensive experience of the influenza bacillus as a background, and the large material of the Department of Health available, carefully chose their cases and controls. The first group studied consisted of early cases occurring in a children's home, many in the first day of the disease. These all showed almost pure cultures of influenza bacilli. Ninety-eight per cent of the later cases in this home also showed the bacilli. The only fact which detracts from the significance of the high percentage in this series is that a number of cases of whooping cough had existed in the institution during the preceding summer. In their next group they studied 30 marines who had just come to New York in a body, and were cultured almost immediately upon the establishment of the diagnosis. In all of these influenza bacilli were found, and in these cases both whooping cough and measles, diseases with which the influenza bacillus is so often associated, could be definitely excluded. At about the same time Park and Williams obtained 34 cultures from a girls' home in which there had been no influenza, and found the organisms in two of these only. In a similar institution where there had been a number of influenza cases, 33 per cent of the inmates harbored the bacilli. Of 30 autopsy cultures, influenza bacilli were found in the lungs in 24, and in 5 of them they were in pure culture; the bacilli were also present, in considerable numbers, in 26 out of 27 tracheas examined. In 40 per cent of the cultures taken from nurses who had been in contact with cases, influenza bacilli were present, whereas, those that had not been in contact with cases showed them in 9 per cent only. Of all the studies which have resulted from this epidemic those of Park and Williams and their assistants are perhaps the most encouraging to the assumption of the etiological importance of influenza bacilli. And yet as Park himself points out, the bacilli were also found in 67 per cent of measles cases examined at about this time.

We would not be doing justice to the problem as a whole did we not include in our analysis of the bacteriological findings an account of some of the other bacteria which have been described by observers as perhaps having

etiological relationship to the disease. In a malady in which the secondary invaders give character to a large majority of the severe cases, it is to be expected that many different organisms should be described. Mathers at Camp Mead found an unusual number of cases in which the predominating organism was a Gram-positive diplococcus probably belonging to the streptococcus group. This organism was found by Jordan in cases studied in Chicago. Orticoni isolated an aerobic non-motile bacillus from influenza cases, and from an epidemic of so-called influenza which occurred among horses in the same neighborhood. In this connection it is interesting to remember that MacNeal and Pease, in their studies of an epidemic at a Veterinary Hospital and Remount Unit at which a so-called influenza epidemic among the horses coexisted, were able to exclude any connection between the two outbreaks.

Fry in 1919 isolated oval Gram-negative yeast-like bodies from the blood of two German prisoners which upon subculture, took the form of small Gram-negative bacilli. He speaks of them as "Pfeiffer-like" organisms which, however, were not hemophylic and grew rapidly on ordinary agar. With this organism Fry and Lundie later claim to have made an antigen which gave specific complement fixation with influenza blood. Edelmann in Vienna on several occasions found paratyphoid "B" bacilli in the blood and intestines (!) of influenza cases.

The many reports in which pneumococcus and streptococcus have been found as predominating organisms we may dismiss without analysis since all investigators will now agree that no specific etiological significance can be attached to these bacteria.

Of more than passing interest, however, are the frequent reports of Gram-negative micrococci of various kinds. Most of the workers in this country have commented upon the frequency with which micrococcus catarrhalis and other Gram-negative cocci closely related to this organism have been found in influenza sputum. In our own work, especially during the Baccarat epidemic we noticed the great number of cases in which Gram-negative micrococci seemed to predominate in smears and cultures of the pharynx and throat. We were not able, however, to study these organisms in detail at the time. Kinnicutt and Binger, who worked during July and August of 1918 at an American Base Hospital in France have reported a series of cases in which the predominating organisms were true meningococci. They describe two epidemics, one which occurred at Mirmizan in the Department of Landes, in which there were 350 cases among 553 men, and 30 bronchopneumonias with 15 deaths. Another outbreak occurred at Le Courneau, Department of Gironde where there were 3915 cases with

275 pneumonias and 65 deaths. The epidemics began as the typical mild fever, rapidly becoming complicated and ending with many severe cases. In the first epidemic they took a considerable number of blood cultures all of which were negative except one which showed meningococci of type C (Pasteur Institute serum). Four out of 10 autopsies showed meningococci in the lungs. In the Le Courneau epidemic they took 25 nasopharyngeal cultures, 22 of which showed Gram-negative diplococci. Of 14 strains so obtained, 9 were true meningococci as tested with agglutinating serum. They took 4 cultures of sputum, all of which showed Gram-negative micrococci and 2 of which agglutinated like true meningococci. Of 15 blood cultures, they obtained 4 Gram-negative diplococci, 3 of which agglutinated like true meningococci. Of 24 heart's blood cultures, 4 showed similar organisms, 3 of which were proved by serum. Of 22 cultures from the lungs, 12 showed Gram-negative diplococci, 5 times in almost pure culture; and 11 of these strains agglutinated like meningococci.

In another epidemic at St. André de Cubzac they took 29 cultures, 55 per cent of which showed Gram-negative diplococci. Only 3 of these cases showed Pfeiffer bacilli.

Fletcher in 1919 reported studies on autopsies of 36 American soldiers who died of bronchopnuemonia following influenza. In 11 of the 36 cultures taken from the lungs he found Gram-negative diplococci on blood plates, and most of these turned out to be meningococci of Gordon types I and II. Fletcher, however, also found a considerable number of cases in which influenza bacilli were present without meningococci.

Similar findings have been reported by Leitner and by Trawinski and Cori in Vienna.

It is of course difficult to make any conclusive statements about findings of this nature. There can be no question about the fact that observations so reported are accurate, and, indeed, any one who has studied the bacteriology of cases of this kind knows that the manifold nature of the flora of the respiratory passages which normally exist is tremendously enhanced in the presence of a catarrhal inflammation. It would seem to us judging from experiences such as those of Kinnicutt and Binger, from our own observations, and from reports made from various camps and base hospitals during the war that the nature of the flora of the nose and throat may take on a local character owing to infection from man to man under crowded military conditions. The predominance of streptococci in one place, pneumococci of a particular type in another, and Gram-negative micrococci at again another would necessarily influence the bacteriology of the fatal infections. During the first year of the American entrance

into the war, this was noticed at training camps where streptococcus pneumonias or infections with pneumococci of types I or II, often predominated numerically as secondary invaders in measles, etc.

That influenza, whatever its etiology may be, increases susceptibility to invasion with all sorts of other bacteria cannot be questioned. As far as the meningococcus observations are concerned, these may well be explained by greatly increased susceptibility to this organism, induced by influenza and coincident with a high meningococcus carrier rate. Carrier rates in troops of 10 and more per cent have frequently been observed by Gordon, Glover and others, and we ourselves have seen a number of cases which began as typical influenza and ended as meningococcus sepsis or typical meningitis.

Because of the great complexity of the etiological problem we believe it wise, at the end of each block of reported data, to outline tentative summaries of the evidence so far presented. Surveying, therefore, the purely cultural work which has been done on the influenza bacillus since 1889, we may now add to the statements made in a preceding summary that the bacteriological studies made during the pandemic of 1918 and the following years have confirmed the fact that influenza bacilli may be found in a very large percentage of early and late cases of influenza; that they have been found by Park and his collaborators, by Deitrich, Schmidt and, in a similar series, MacNeal and ourselves, in 100 per cent of early cases: and that a great many of these workers have found them as the predominating organisms in cases with pulmonary complications; they have also been found by a considerable number of investigators in pure culture in autopsies of fatal cases. They have been found more frequently than any other organism in connection with the disease in all its stages.

By some investigators the organism has been found in the throats of contacts in a higher percentage than in those of non-contacts.

The failure of many investigators to find the organisms in simple cases in the early stages of the epidemic may well have depended upon the same difficulties that determined our own early failures, namely, insufficient attention to cultivation from the nasopharynx (owing to the absence of or the mild character of subjective symptoms referred to this locality) and perhaps imperfect cultural technique.

Failure to find the organisms in blood cultures in these early cases has been practically universal, and might be considered a strong argument against the etiological significance of the influenza bacillus, because these early cases suffer from serious systemic symptoms in spite of their mild local lesions. We do not feel confident ourselves that the blood culture failures are sufficiently conclusive to warrant the assumption that the organisms are absent from the blood stream, since there have been isolated instances of positive blood culture results even in apparently uncomplicated cases. A few such have been reported by British observers during the early phase of the 1918 outbreak and there are many technical reasons why it may be very difficult to cultivate these organisms from the blood stream.

Moreover, recent observations upon the powerfully poisonous products that can be obtained in influenza cultures, made in our own laboratory by J. T. Parker and confirmed by Huntoon, Wollstein, and others indicate the possibility that a severe systemic disease may well be explained by a relatively small influenza lesion in the throat.

It is plain from cultural studies alone that the influenza bacillus is either the cause of influenza, or that it is an almost universal complicating invader, which gains a foothold in the body almost immediately upon the establishment of the original infection. The decision concerning this must eventually rest upon the same grounds that will decide for us whether the mild sore throat and bronchitis that occur in most, and perhaps in all cases, are complications or represent a part of the basic disease.

One of the great difficulties in the way of formulating final conclusions is the great frequency of influenza bacilli as harmless saprophytes and as secondary invaders in measles, whooping cough, etc., during non-epidemic periods. This, it is true, is a puzzling phase of the problem which must receive much further study. While, on the one hand it tends to weaken any positive etiological conclusions, on the other hand it might be explained by acquired immunity in the invaded subject, by fluctuation of virulence in individual strains of bacilli, or by a multiplicity of races.

The bearing of serological evidence on etiology

We might expect to obtain indirect light upon the problem of etiology from investigations of specific antibodies for the influenza

bacillus in the blood stream of patients during and following the disease. This line of investigation has been taken up by a considerable number of workers. Thus, Loewenthal in 1918 found that his cultures were agglutinated up to 1 to 400 by the serum of his patients. He claims that the agglutination reaction may be of specific diagnostic value. Similar claims have been made by others. But there have also been a considerable number of contradictions, and during the last few months the entire question of specific agglutination in the influenza group has been in a state of great confusion. The problem is interwoven with the question of the antigenic uniformity or multiplicity of the Pfeiffer group, a problem which must be discussed briefly before we can pass judgment upon the value of the "antibody" evidence.

In 1915 Wollstein made a comparative study of different strains of the influenza bacillus isolated from various sources. She found that there was a wide difference, in pathogenic power for animals, of influenza bacilli isolated from different processes in man, Those obtained from the blood and meninges and some of those obtained from pneumonic lungs were highly pathogenic, while those from the upper respiratory passages were less so. So far as agglutination, complement fixation, and opsonin tests were concerned, there was no sharp difference between these two classes, and she concluded that in spite of differences in pathogenicity, all these organisms belonged to the same class or race, irrespective of origin. In 1919, Rappoport studied complement fixations by the serum of influenza patients with influenza bacillus antigens. He found 54.5 per cent positive fixations with sera of such cases, in contrast to a percentage of 9.67 per cent of 30 controls. Kolmer, Trist, and Yagle made similar observations on influenza cases, using a number of different antigens, one of which consisted of influenza bacilli, and found that 45 to 50 per cent of their sera reacted with the Pfeiffer bacillus, whereas 38 per cent reacted positively with streptococcus and micrococcus catarrhalis antigens. Wollstein carried out a similar series of studies, first attempting agglutination, a method which she subsequently abandoned because she found it unsatisfactory and irregular. She then did complement fixations in which she used antigens consisting both of bacilli suspended in salt solution and of heated broth cultures. By this method

she found that normal controls did not fix complement in the presence of the antigen, but that the blood of recovered patients gave reactions in dilutions varying from 1:5 to 1:20. She found that it was necessary to use more than one strain of the organisms, in order to obtain regular results. Her reactions appeared constantly at the end of the first week, increased in intensity for two weeks, and remained demonstrable for as long as from two to four months. Of great importance is her observation that the antigens prepared with the epidemic strains were serologically similar to those produced with strains isolated from influenza cases in interepidemic years, differing from them only in quantitative relations. She draws no definite conclusions, but says: "The patient's serological reactions indicate the parasitic nature of the bacillus, but are not sufficiently stable and cleancut to signify that the Pfeiffer bacillus is the specific inciting agent." And further below: "Its presence influences the course of the pathological process."

A short time ago in our own laboratory similar complement fixation tests were carried out with convalescent influenza sera by Mrs. Parker, experiments in which as many as six different antigens were used on every serum. It was found that a large number of supposedly normal sera gave fixations as powerful as those obtained from convalescent cases. Although the cessation of the epidemic prevented the completion of this work, it was so carefully done and controlled that it has persuaded us that complement fixation is at any rate not sufficiently sharp to throw conclusive light upon the problem.

An astonishing and confusing turn has been given investigations of this nature by the agglutination experiments carried out by Valentine and Cooper in the New York Department of Health Laboratories. These workers isolated organisms from autopsies and active influenza cases and then attempted to classify them by agglutination reactions. Their primary purpose was to find out whether there was any single epidemic strain, and they paid particular attention to those strains which were obtained from lungs at autopsy and other lesions in which it seemed fairly definite that they were not dealing with saprophytic habitual symbiants. It is impossible to detail all their results, but it is sufficient to say that they found a surprising multiplicity of races. The following examples may suffice to indicate the degree to which

this was true. Of 10 autopsy strains no two were found alike by agglutination. One autopsy strain was identical with one of the miscellaneous strains, and another autopsy strain was identical with another of the micellaneous ones. Of 73 miscellaneous strains, no two were found to be identical. Of 54 strains obtained from military patients, only 2 strains from different individuals were found identical. But in one case the third day isolation was identical with the seventh day, but the one on the fourteenth day was different. Of 28 strains obtained from a Hebrew orphan asylum only 2 were found to be identical. And of a family of 6, from each member of which an organism was obtained, all the strains were found to be distinct. Park states that in 9 of the autopsy strains the "unlikeness" of the strains was so sharp that absolutely no cross-agglutination took place.

Bloomfield who introduced influenza bacilli into the nasopharynges of normal people, states that in 5 instances which he isolated influenza bacilli more than twenty-four hours after he had introduced them, the organisms recovered differed from those introduced, the tests applied being the biological differential methods suggested by Rivers. The strain introduced was in some cases an indol former and agglutinated with stock sera, whereas the recovered strain formed no indol, and did not agglutinate with the serum. In another case the strain introduced was non-hemolytic and formed no indol, whereas, the one recovered from a tonsillar crypt after four days was hemolytic and formed indol.

It is plain even from the few investigations that we have mentioned that no help can be expected at this time from serological investigations. The agglutination reaction is obviously useless for this purpose at the present time. When investigators as careful and experienced as Park and Williams and their assistants report six different agglutination types from six members of the same family, the first thought that comes to us is not that these strains are all different, but rather that agglutination in this group, for some reason or other (perhaps because of the minuteness of the organisms, and peculiar surface tension relations), is not specific; and the frequency with which normal sera have fixed with influenza bacillus antigens of six different races in our own laboratory, leads us to believe that complement fixation too is a method of small promise in this problem. And even

though specific antibody reactions could be regularly observed in active and convalescent cases, it is doubtful whether this would show much more than the organism is pathogenically significant; whether as the original etiological factor, or as a secondary invader, however, would still be in doubt.

Evidence derived from vaccination

Another set of observations which must be included in our consideration of the etiological importance of influenza bacilli, are those which deal with artificial immunization or vaccination, prophylactically employed during influenza epidemics. Such evidence would possess the same indirect value as antibody investigations, in that protection with influenza vaccines would indicate specific relationship. Such investigations are fraught with many possibilities of error, since during an epidemic it is difficult to safeguard the vaccinated and the controls from accidental infection, and to impose upon them conditions which would approach experimental accuracy.

The general impressions of Park who thoroughly realizes the difficulties attending accuracy in such work, are unfavorable to the assumption of any protective effect.

Eyre and Lowe inoculated 16,000 men, leaving 5700 controls which were either uninoculated or had received only one dose. The vaccines contained pneumococcus, streptococcus, influenza bacilli, staphylococcus aureus, micrococcus catarrhalis, Friedlander bacilli and a bacillus which they call bacillus septus. They tabulate their results as follows:

	per cent
Incidence among inoculated	1.3
Incidence among uninoculated	4.1
Mortality among inoculated	0.26
Mortality among uninoculated	2.2

Cadham in 1919 reported studies in which he used mixed vaccines of streptococcus, pneumococcus and influenza bacilli upon soldiers. He claims that the incidence of pneumonia was one-half and the mortality less than one-third among the inoculated as compared with the uninoculated. The mortality of inoculated soldiers was 2.5 per 1000, whereas, in the town nearby among the general population it

was 6.28 per 1000. This particular experiment proves nothing in our opinion, since the mortality in influenza is generally due to secondary infections, and since the soldiers were all vigorous young people, while the inhabitants of the town included the aged, tuberculous and very young.

Wirgman in the same year reported observations upon 11,000 people of whom 800 were inoculated in November and December, 1918, and January, 1919. His figures are as follows:

	per cent
Incidence among inoculated	5
Incidence among non-inoculated	10
Death rate among inoculated	0
Death rate among non-inoculated	19

Friend reports observations at a public school in West Horsham made during this epidemic. Of the boys 633 were inoculated and 186 uninoculated. The school remained free of influenza, although the disease was prevalent in West Horsham itself. But it is recognized by Friend that physical training, careful supervision, hygiene, and good nutrition played important rôles in holding down the sick rate.

McCoy in a criticism of vaccination in influenza has pointed out a number of significant sources of error in such investigations. The chief one of these lies in the fact that the inoculations have usually been done during the progress of an epidemic and that the case-incidence among the inoculated has been compared with the case-incidence among the general population or controlled groups calculated from the beginnings of the epidemic. It is obvious that a number of the cases in the general population may have occurred before the vaccine was given, and among the vaccinated are included a number of people who are probably insusceptible. Also he points out that a vaccine cannot ordinarily be expected to have any appreciable prophylactic effects in less than seven or ten days after it is given, and considers that the only fair comparison is one which takes into account calculations on vaccinated and unvaccinated beginning ten days after the vaccinations have been made. In summarizing the evidence he selects a number of instances in which these criteria have been observed. Thus Hinton and Kane vaccinated about one-half the patients is an epileptic colony, the vaccinations being completed

some ten days before the disease became prevalent in the institution. The vaccine contained 8,000,000 bacilli per centimeter, and a total of 2,000,000,000, was given to each person. There were 461 people vaccinated, and 538 not vaccinated. Among the vaccinated, there was a morbidity of 35.4 per cent, with 17 per cent deaths, while among the unvaccinated there were 34.3 per cent cases with 13.5 per cent deaths. A similar experiment was done on naval personnel at the Pelham Bay Training Station (Notes on preventive medicine for medical officers, United States Naval Bulletin, nos. 50 and 51). Nine per cent of the 154 inoculated, and 5 per cent of the 800 uninoculated developed the disease. Similar results were obtained at a naval base in South Carolina. McCoy reports a few experiments carried out in various institutions by members of the United States Public Health Service in which a comparison between 484 vaccinated and 842 unvaccinated controls were made. Among the vaccinated there were 31.6 per cent cases, with no deaths, and among the unvaccinated there were 26.3 per cent cases with 1.8 per cent deaths. In this case the vaccine was a pure influenza bacillus suspension.

We may summarize this phase of the work, in complete agreement with McCoy, to the effect, that, in spite of the general impression favoring the value of vaccination in the prevention of influenza, gained from the study of poorly controlled experiments, the evidence furnished by experiments that have been controlled in every particular has so far failed to demonstrate any effects whatever upon either incidence of mortality.

Inoculation experiments

The most perfect proof of the etiological relationship of influenza bacilli with the disease could of course be obtained by the production of the typical disease in normal human beings by inoculation with pure cultures of influenza bacilli. During the earlier pandemic it seemed that certain laboratory accidents had definitely indicated that such transmission was possible, the one most frequently cited being the laboratory infection of Kretz whose nose touched a plate he was fishing, and who in consequence developed an acute inflammation of the respiratory passages with influenza bacilli persisting in his sputum for several months. In such cases, however, just appraisal of the

evidence is difficult because these accidents occurred during an epidemic or its early post-epidemic periods and happened to individuals the nature of whose work brought them into contact with infectious material. Also the symptoms described were usually those of localized catarrhal inflammations rather than of true influenza. Purposeful and well controlled experiments upon man would be more conclusive and extensive attempts in this direction have accordingly been made by a number of investigators during the last pandemic.

Since typical influenza cannot be produced in any of the lower animals, the only species which besides man are worth considering for such work are the monkeys and the higher apes. Within recent months Cecil and Blake working at the United States Army Medical School in Washington, have succeeded in producing typical lobar pneumonias by intratracheal inoculation of pneumococci in various species of monkeys. This encouraged them to experiment upon these animals with pure cultures of influenza bacilli. They used a Philippine monkey, Macacus Syrichtus, and a Central American species, Cebus Capucinus. The strains of Pfeiffer bacilli employed were isolated from an influenzal pneumonia in a child. The virulence of the strains, which has been on artificial media for six weeks, was raised by successive mouse passages and subsequent intraperitoneal passage through a series of 13 monkeys. They then inoculated a group of 22 monkeys. The material used for inoculation consisted of first or second subcultures of organisms isolated from animals dead of pneumonia or peritonitis, and of peritoneal exudates from such animals, used directly from the body.

In some monkeys the material was introduced into the nose by application with a sterile cotton swab or with a pipette. In another group the material was introduced low down into the trachea by injection with a syringe.

Twelve monkeys were inoculated by the nasal method and in every instance acute respiratory disease developed; three to five hours after inoculation there was prostration, in some cases with a temperature of from 103° to 106°F. in others there was very little or no fever. Sneezing, rubbing of the nose and other signs of catarrh became manifest. In most cases at the end of twenty-four to forty-eight hours the infection spread to the lower passages and a cough developed.

Five of the monkeys developed acute sinusitis from which the influenza bacillus could be obtained. Two animals developed pneumonia on the third and fourth days, and the influenza bacillus was obtained in pure culture from the lungs. Ten monkeys received intratracheal injections of 1 to 5 cc. Again prostration and temperature developed in most of them with respiratory symptoms. In one case general infection with speticemia and pericarditis ensued. None of these died. Seven developed pneumonia and were killed during the active stage, and from the lungs influenza bacilli in pure culture were recovered. The pneumonia which developed was widespread, and lobular in type, with extensive hemorrhage and edema appearing to Blake and Cecil similar to that occurring in man.

The experiments of these investigators show that the bacillus of influenza can produce a violent infection of the upper respiratory tract with catarrhal symptoms and other manifestations, common in man at the time of prevalence of influenza epidemics. There can be no doubt about the fact that these experiments add considerable weight to the assumption that the bacillus of influenza causes the disease in man. We will recur to this in our final discussion of this phase of the general evidence.

More directly pertinent are inoculation experiments on man. David J. Davis in a letter written to the Journal of the American Medical Association of May 3, 1919, writes that in 1906, having isolated influenza bacilli from a considerable number of cases of whooping cough, measles and varicella, he inoculated a young healthy man with pure cultures of the bacilli. Preliminary cultures showed no similar organisms in the subject's throat; he had had no serious illness of any kind within the immediately preceding period. The washings of 6 blood agar tubes were taken up in salt solution and the throat, tonsils, and nasal mucosa were smeared with the suspension. Forty-eight hours after the inoculation he complained of chilliness and great weakness. A temperature of 100.2° developed, but rapidly subsided, returning to normal on the third day. He complained of headache, general malaise, and coughed slightly. The throat was slightly congested, and the pharynx coated with thick, stringy mucus. The local condition persisted for about four weeks during which there was a very slight cough which did not in any sense resemble that of

whooping cough. During the first few days an almost pure culture of influenza-like bacilli was recovered. In the course of the next three weeks the influenza bacilli gradually disappeared from the throat. There were no complications. The description of this case, as given in Dr. Davis's letter has certain important points of similarity with early cases of epidemic influenza, especially as regards the mildness of the local symptoms with the sudden development of temperature, severity of the systemic symptoms and short duration of the fever.

In 1919, Rosenau, McCoy and collaborators, working under Government auspices, carried out a series of important experiments on man carefully controlled and elaborately planned. The group conducting the investigation were officers of the United States navy and of the Public Health Service; McCoy, Goldberger, Leake and Lake on the part of the Public Health Service, coöperating with Rosenau, Keegan and Richey, on the part of the United States navy. The experiments were carried out at Gallops Island, the quarantine station near Boston. The volunteers were all between eighteen and twenty-five years of age and in good physical condition. Of the 100 men used, none of them had had influenza or any febrile attack during the preceding winter. Preliminary experiments in which pure cultures of the influenza bacillus in moderate amounts were instilled into the nostrils of a few of the volunteers were entirely negative. In consequence, a more drastic experiment was decided upon. Nineteen volunteers were given a considerable quantity of a mixture of 13 different strains of Pfeiffer bacillis, some of them recently obtained from the lungs at autopsy, others representing subcultures of different culture-generations obtained from recent cases. Suspensions of the bacteria were sprayed into the nostrils, eyes, and throats with atomizers while the volunteers were inspiring. Several billions of the organisms were used on each one, but not a single one of them developed any kind of illness.

Following these negative experiments an attempt was made to infect directly with mucous secretions obtained from the mouths, noses, throats, and bronchi of active cases of influenza. The material was obtained from febrile cases by washing out nostrils and throats with 5 cc. of salt solution and allowing the patient to blow his nose

vigorously into a sputum dish. They were then made to gargle with some of the solution and this was added to the rest. Bronchial mucus was obtained after coughing, and the nares and throats were swabbed. The swabs with all the materials were then put into bottles with glass beads, and this (properly called "stuff" by Rosenau) was administered to the volunteers. Ten men were used and each of them received about 1 cc. sprayed into nose and throat while inspiring, and into the eyes. None of them became sick. Other experiments done at this time by the same Board will be recorded when we come to speak of filtrable virus. Most astonishing of all of the work done by this Board are the entirely negative attempts to infect such volunteers by bringing them into the closest possible direct respiratory contact with cases in the active stages of the disease.

McCoy and Richey carried out similar experiments at Goat Island in San Francisco Harbor, also with entirely negative results.

It is very difficult to comment upon these experiments. Their completely negative character would lead one to assume not only that influenza bacilli did not convey the disease, but the upper respiratory secretions of influenza patients were not the vehicle of infection. The latter conclusion can hardly be credited in view of the large volume of epidemiological evidence in favor of such transmission; and when we consider the experience and reliability of the investigators who carried out these experiments we must assume that some third factor, the most likely one being insusceptibility on the part of the volunteers must have played a part. Even this, however, would seem unlikely in view of the large number of men used and the careful scrutiny made before the experiment. As a matter of fact there is no satisfactory explanation for these failures at the present time.

Wahl, White and Lyall in 1919 also applied saline emulsions of fresh Pfeiffer strains from epidemic influenza cases to the nares and nasopharynges of 5 healthy men, absolutely without success; and these investigators did not succeed, except in a single case, in recovering the influenza bacilli from the nares forty-eight hours later. To this point we will refer in our summary since we consider it of considerable importance.

Bloomfield, investigating more particularly the length of time during which influenza bacilli would persist in the upper respiratory pas-

sages of healthy individuals, introduced 3 different strains of influenza bacilli in large amounts into the upper air passages, and in none of his 5 cases observed any local or general pathological effects. Moreover Bloomfield found that the organisms disappeared within from one to two days, and that a carrier state was produced in none of them.

Yamanouchi, in connection with his experiments on filtrable virus, has reported completely negative experiments with the Pfeiffer bacillus in man.

Lister and Taylor though unsuccessful with filtered material, inoculated 5 controls with unfiltered material from influenza lungs. Two of these had typical attacks of influenza, coming down with the disease thirty-six hours after the material had been instilled into the nasopharynx. One volunteer was sprayed with a pure culture of influenza bacilli and came down with a "mild attack."

More recently, Cecil reported to the Medical Section of the New York Academy of Medicine (May 19, 1920) a few experiments in which he introduced Pfeiffer bacilli (the virulence of which had been raised by methods analogous to those used in his previous monkey experiments) into 6 persons. He obtained moderate local and systemic symptoms which suggested very mild influenzal attacks, curiously enough there was absolutely no temperature in any of them.

Attempts to produce typical influenza with cultures of influenza bacilli have, therefore, been negative in most cases. With the exception of the few instances of apparent success by Lister and Taylor and the last suggestive experiments of Cecil no encouragement has been obtained along these lines. But it should be remembered that it has been shown that it is extremely difficult (as in Bloomfield's work) to induce the influenza bacillus to gain a foothold on the normal mucosa, and negative experiments cannot be taken as conclusive until a failure to obtain symptoms persists in spite of the establishment of the organisms in the inoculated throats for at least forty-eight to seventy-two hours.

Filtrable virus

Before we can attempt to summarize views on the etiological importance of the influenza bacillus, it becomes necessary to consider in some detail a series of investigations inspired by the suggestion that influenza may be due to a filter-passing virus.

The thought that such a virus might be responsible for influenza is suggested by the nature of the mild cases which appear early in epidemics, the extreme infectiousness of the disease, and the lack of uniform bacteriological findings in such early cases. Moreover, the clinical similarity of the catarrhal features of mild grippe with the ordinary common cold, in which the work of Kruse, Foster and others has indicated a possible "filtrable virus" etiology aroused hopes of similar "leads" in the influenza problem.

In October, 1918, at the Academy of Sciences in Paris, Nicolle and Lebailly made a preliminary report on studies which later they described in detail in the Annales of the Pasteur Institute. These workers first inoculated mice and guinea pigs, intraperitoneally and intracerebrally, with blood and secretions from a typical case of uncomplicated grippe. These attempts were unsuccessful. They then inoculated nasal and buccal secretions of a typical case into the conjunctiva and the nasal cavities of several monkeys (Macacus Sinicus) using the secretions both filtered and unfiltered. At the same time they inoculated two healthy human beings. The monkeys became sick in six days with a temperature of 40°C. and with diarrhea and great depression. Both of the human beings who had been subcutaneously inoculated with the filtrate became ill at about the same time, and in the same way as the monkeys. Blood from the first monkey was injected into a man twenty-two years old without result.

Subsequently, they injected blood of a typical case into a man intravenously. The result was doubtful, but this subject was older than the others, a fact to which they attribute their partial failure. They concluded that: (1) Influenza secretions are virulent. (2) Macacus sinicus and Cynomologus are susceptible by conjunctival and nasal inoculation; (3) the agent is filtrable since the filtered secretions produced disease in 2 human beings after subcutaneous inoculation. (4) intravenous inoculations and blood inoculations are unsuccessful; (5) virus is easily destroyed by drying or by prolonged exposure to conditions outside the body.

At about the same time Dujarric de la Riviere took blood from 4 severe influenza cases and after dilution filtered it through Chamberland filters. He injected himself subcutaneously with 4 cc. of this

filtrate. On the third day after the inoculation he developed intense headache, pains in the limbs, chilliness and weakness. His temperature went to 38°C. and fluctuated from then until the fifth day, after which he rapidly improved; great weakness and cardiac disturbances remained. He seemed to be immune to subsequent inoculations of the sputum filtrate sprayed into his nose and throat.

Selter in 1918, failing to find influenza bacilli with any regularity, tried the same thing. He filtered nasopharyngeal mucus and gargle water of patients early in the disease, through Berkfeld filters, and sprayed his own throat and that of a woman assistant with this material, both of them inhaling the spray. In both cases a "mild influenza" resulted within seventeen to twenty hours.

Binder and Prell in the same year described minute bodies smaller than cocci in the tissue spaces around the vessels of the lungs in all cases of influenza and failed to find similar bodies in other pulmonary infections. These coccoid bodies were as small as those described by Noguchi in poliomyelitis, and could be stained by iron hematoxylin and Giemsa, but not by Gram. They believed that they could cultivate these bodies in serum-sugar-broth, but were extremely cautious in drawing etiological conclusions.

V. Angerer, soon after this, inoculated rats with the serum of influenza cases. When the animals became sick he filtered their blood, and cultured the filtrates in glucose bouillon. In these cultures he found minute granules similar to those described by Binder and Prell. Similar bodies he claims to have cultivated directly from the serum of human influenza cases. He, too, was extremely cautious in drawing conclusions from these findings.

In October, 1918, Bradford, Bashford, and Wilson published results of studies upon six diseases including trench fever and influenza in which they claimed to have shown that filter-passing organisms were involved in all of them. With their filtrates they produced illness in guinea pigs and monkeys; and in anaerobic cultures prepared by a modification of the ordinary technique employed for Treponema pallid they observed certain small Gram-positive bodies which they regarded as the causative agents.

Similar, though less extensive experiments were reported by Gibson, Bowman and Conner.

Later, Arkwright who had been working along the same lines criticized the results of Bradford, Bashford and Wilson, reporting negative experiments carried out by the war office upon three volunteers inoculated with the supposed cultures of Captain Wilson. He also pointed out the frequency of the appearance of small coccoid bodies in control tubes of media prepared by the method used by the other investigators. Indeed, the almost regular observation of cloudiness and of minute coccus-like bodies in tubes prepared by the anaerobic method mentioned above has puzzled many workers in the past. We have noticed it again and again in work with syphilis and poliomyelitis and are quite sure that it is dependent upon the action of the tissue enzymes upon the protein of the medium. Bradford and Wilson admit the inconclusiveness of their results, at least as far as the minute bodies are concerned, in statements appended to Arkwright's article.

In 1919, Yamanouchi, Sakakami and Iwashima reported experiments on the filtration of influenza virus which, if they could be completely accepted, would settle the entire matter, conclusively. These results were as follows:

1. An emulsion made of the sputa of 43 influenza patients in Ringer's solution was injected into nose and throat of 12 healthy people.

2. Filtrates of the same emulsion was injected into noses and throats of 12 other healthy people. Six who had already had influenza showed no symptoms, but all of the other 18, those who had had the emulsion and those who had had the filtrate, came down with the disease after an incubation of two to three days.

3. Filtrates of blood of influenza patients were injected into noses and throats of 6 other healthy people with similar positive results.

4. Filtrates of sputa were inoculated into 4 healthy people; and 4 others received filtrates of the blood of influenza patients subcutaneously. All of them developed the disease after two or three days with the exception of the one who had had influenza.

5. A pure culture of Pfeiffer bacilli and a Pfeiffer bacillus culture mixed with pneumococci, staphylococci and streptococci was injected into nose and throat of 14 healthy people who had not had influenza. No symptoms followed these injections.

Lister and Taylor working in South Africa filtered material from the lungs and throats of typical influenza cases and instilled the filtrates into the nostrils and throats of human volunteers and monkeys. *All were negative.* Of 5 controls receiving unfiltered material, 2 had typical attacks of influenza 36 hours after inoculation. All the monkeys, even those that received unfiltered material, remained well. They sprayed the nasal passages of one volunteer with a pure culture of influenza bacilli, and in this case a "mild attack" resulted.

Wahl, White, and Lyall in 1919 sprayed the nasopharyngeal cavities of several men with Berkfeld filtrates of material from pneumonic lungs of typical influenza cases, with entirely negative results.

Leschke, in the same year, used bronchial secretions and juices expressed from the lungs of influenza cases and filtered them through Berkfeld filters. He inoculated these into ascites broth. After forty-eight hours, minute round bodies were noticed which could be stained with heated concentrated carbol fuchsin and were Gram-negative. They could not be transferred successfully to new cultures, but these minute bodies were also visible in bronchial sercretions of dead influenza cases as well as in lung sections. Lung filtrates, incubated for several days and vaporized, were inhaled by a number of people for several minutes. These individuals came down with "typical influenza!"

Fejes (in 1919) filtered the sputum of influenza pneumonia cases and iniected it subcutaneously into rabbits and guinea pigs without result. The same material was injected on four separate occasions into monkeys, two monkeys being used in each experiment. In these cases one monkey was injected with the material immediately after filtration, and the other after heating for one hour at 65°. The animals that received the heated filtrate remained well. All the monkeys treated with the unheated filtrate died several days after the inoculation, with clinical and pathological appearances of general hemorrhagic sepsis. The material from which the filtrates were made showed in one case a pure pneumococcus, in the second a streptococcus hemolyticus, and in the other two mixed cultures with Pfeiffer bacilli. The bacteriological analysis of the animals that died is unsatisfactory as described.

Minute bodies in smears of throats, noses and exudates of influenza cases also have been described by Kronberger and Poppelmann.

Experiments made by the United States Public Health Service and the United States navy under the direction of Rosenau and McCoy are among the most extensive that have been carried out upon human beings. They have been referred to, in part, in a preceding section. After unsuccessful attempts to produce the disease with pure influenza bacilli, they instilled filtered nasopharyngeal mucus from fresh cases into the tonsils, throats and eyes. The results were entirely negative. Subcutaneous inoculation of similar filtrates into 10 volunteers, each one receiving 3 cc., were entirely unsuccessful. Negative results were also obtained when blood was injected and when the volunteers were brought into close respiratory contact with active cases.

In the May 29 issue (1920) of the Journal of the American Medical Association, Olitsky and Gates published a series of experiments also dealing with a filtrable infectious agent in influenza. They used filtered and unfiltered influenza secretions, and filtered and unfiltered lung tissue suspensions prepared from previously inoculated rabbits. The inoculations were carried out directly into the lungs by means of the intratracheal catheter, 3 cc. of the material being used for rabbits weighing from $2\frac{1}{2}$ to 3 kgms. From 7 to 8 fresh cases, that is cases less than thirty-six hours old, they obtained definite effects in rabbits which they describe as follows: Within twenty-four to forty-eight hours after inoculation, fever developed, with listlessness and general illness of the animal. With this there was conjunctivitis and a marked leukopenia. These symptoms lasted for about three days, after which the animal returned to normal. They never died except in cases where obvious secondary infection had taken place. When killed during the period of illness, the respiratory organs alone showed pathological changes. The lungs were enlarged and edematous, and often hemorrhagic. There were hemorrhagic foci on microscopic sections, and there was a cellular exudate in the alveoli. Controls made by many different methods failed to show similar effects. After this, repeated filtration did not interfere with the effects described above. The agent, whatever it was, seemed to resist 50 per cent glycerine for nine months. They draw very conservative conclusions.

Since the first writing of this paper, Olitsky and Gates have con-

siderably extended their researches by further animal inoculations and cultivation experiments by anaerobic methods corresponding to those used in treponema cultivation, namely, anaerobiosis with tissue and ascitic fluid. They have cultivated from filtered nasopharyngeal washings of influenza patients in the first thirty-six hours, a minute bacilloid body capable of indefinite propagation on artificial media, which they have named the bacteria pneumosintes because of its peculiar pathological reactions in lung tissue. They have also recovered this organism from the lungs of infected rabbits. This minute Gram-negative bacillus-like organism is apparently strictly anaerobic and retains its virulence for rabbits for only a limited num ber of generations after cultivation from the human body. They obtained it again during the short influenzal wave of the past winter, 1921–1922, and the characteristics of this organism are similar to the original one. After prolonged cultivation, the organism appears considerably larger than one would expect from a filtrable virus, but still they continue to obtain growth from filtrates through N and W filters. Similar but distinctly different organisms of a somewhat larger size and slightly fusiform appearance were obtained from common colds and normal throats. There seems to be no doubt in the writer's mind, after seeing their cultures, that Olitsky and Gates have observed a group of organisms hitherto undescribed, and the relationship of the true pneumosintes to early influenza, its apparent preparatory influence for secondary infection must lead one to take it seriously as one of the possible etiological suggestions. The difficult nature of the entire problem, however, does not permit acceptance of this, though strict attention to their methods and results will be necessary for all investigators who approach the influenza problem when another wave becomes eminent.

Summary of evidence bearing upon etiology

In the course of every scientific investigation, it becomes necessary, from time to time, to classify and analyze the available data in order that there may be a clear differentiation between experimentally determined facts, probabilities amenable to further experimentation and pure surmise. It is a systematization not only of our knowledge but of our ignorance as well. For in subjects as involved as are the

problems of influenza, on which so many different people have written from so many different points of view, the few available facts may easily be lost in an accumulation of clinical and experimental slag.

Conclusions cannot be drawn. But we can segregate the obviously misleading from the proven facts and can perhaps formulate more clearly the directions of study which appear most promising of eventual light.

It is entirely in this sense that we submit the following summary:

Influenza in its simplest clinical form is a mild fever, with sudden onset, characteristic pains in head, back, and limbs, great prostration and a fever curve which rarely lasts longer than three or four days. It is in this form that it usually makes its first epidemic appearance, and, at this stage, causes almost no mortality. The slight sore throat, mild bronchitis and injection of the conjunctivae which are present in a large number of the cases may represent secondary infections or complications, but are more probably characteristic features of the basic disease.

It is the causation of this basic condition which constitutes the true etiological problem of influenza. While it is generally acknowledged that the influenza bacillus appears early in the disease and is present with considerable regularity, it has been suggested that, preliminary to this, there may be infection by some other agent, perhaps a filtrable virus which paves the way for secondary invasion, first by the influenza bacillus, followed by other bacteria habitually present in the upper air passages.

In favor of attributing the entire process to influenza bacilli are: The frequent isolation of the bacilli even from the earliest and simplest cases; the high percentage of influenza bacillus isolations from all varieties of early and late complications; the peculiar distribution of these bacilli in the large and small bronchi in fatal cases; their frequent presence in pure culture at autopsy; the wide distribution of the organisms throughout populations at times of epidemic, and their gradually diminishing frequency in normal and diseased respiratory passages as epidemics fade into the past. Recently acquired knowledge, furthermore, regarding the potent poisons formed by influenza bacilli in culture, permits us to account for the entire clinical complex of the simplest variety of case by the establishment of a relatively

small influenza bacillus focus in the throat or nasopharynx of a susceptible individual.

Against the assumption of the etiological importance of the influenza bacillus are the frequent failures of competent bacteriologists to find the organisms in the early cases, the presence of the bacilli in the throats of normal individuals; their presence in pathological conditions obviously not clinical influenza; their frequent presence as complicating invaders in whooping cough, measles, etc., the antigenic multiplicity of strains isolated at times of epidemic; and the infrequency of positive blood culture findings in early cases. None of this negative evidence is conclusive for reasons that have been indicated in the text.

Investigations on the appearance of antibodies in the serum of cases that are sick with or convalescent from influenza permit of absolutely no conclusions at the present time, owing to the irregularity in antibody reactions done with influenza bacillus antigens, whether the method used be that of agglutination or that of complement fixation. The curious results obtained by Cooper and Valentine show either an enormous multiplicity of influenza bacilli or non-specificity of the agglutination reaction with this group. Experiences with complement fixation have not given uniformly reliable results when human sera were used. Moreover, were we to find an increased concentration of antibodies against influenza bacillus antigens, it would serve to prove nothing more than the pathogenic significance of the influenza bacilli which we know from cultural studies to be present in most cases, and would not help us to decide whether the organism were the primary cause of the disease or merely secondary invader. It would show nothing more than do the frequent positive serum reactions which have been obtained in influenza and in some other diseases with streptococcus antigens.

Protection experiments with vaccines have been absolutely inconclusive; indeed, they seem to indicate that influenza vaccines do not protect to any considerable degree. This, however, throws little light upon the etiological problem since successful vaccination is delicately dependent upon manner of vaccine production, dosage, mode and frequency of administration, and has yielded negative or doubtful results even in diseases in which the etiological problems are settled.

Attempts to produce the disease in human beings with pure cultures of influenza bacilli have been in general unsuccessful. There are, however, a few very suggestive experiments in the literature particularly the isolated cases of Lister and Taylor, of Wahl, White and Lyall, that of Dick and the more recent ones of Cecil, which at least show that occasionally mild systemic illness may follow the introduction of the bacilli. The completely negative results of Rosenau and McCoy and their collaborators, of Yamanouchi and others are discouraging, but if we consider that in such experiments two factors must be simultaneously adjusted to each other in a perfect way, namely, the virulence of the strain and the susceptibility of the individual, it may well be that failure of one or the other of these prerequisites may account for many negative attempts. It is worth noting in this connection, too, that in many cases where negative results were obtained the organisms rapidly disappeared from the nasopharyngeal mucosae of the inoculated individuals; whereas, in those that partially succeeded, as well as in some accidental infections with cultures the organisms remained present for some time, showing that in the former they were quickly removed by the protective mechanism, whereas, in the latter, they were able to establish a foothold.

Although the burden of the evidence so far cited seems to point in the direction of probable causation by the influenza bacillus, it is obvious that there are a number of elements of uncertainty. To these there is added, as a very serious objection, the report from several sources which cannot be ignored, of successful production of an influenza-like disease in human beings with filtrates of influenzal material—the conditions so produced cannot be positively identified as true influenza. Nevertheless, they are sufficiently suggestive to necessitate further experimental study.

This leaves the entire subject in a very unsatisfactory condition. The temptation to draw definite conclusions from material of this kind is always a strong one. But to profess certainty when available evidence does not justify definite conclusions is as serious an error as to put forth inconclusive experimental work, and would serve merely to mask the truth.

One thing seems distinctly worth emphasizing in closing a discussion of influenzal etiology at the present time, and that is the advisa-

bility of constant attention to the entire influenza literature on the part of bacteriologists working in well equipped laboratories with assistants and equipment sufficient to attack large problems of this kind when occasion arises. The problem of influenza etiology will not, in our opinion, be solved at times when influenza epidemics are in full swing or in their secondary or tertiary waves. Solution will come from laboratories that are prepared to pounce upon the opportunity when epidemics are in their adolescence, and bacteriologists will miss this opportunity of swinging their equipments and energies for a few intensive months into this extremely important problem unless they are familiar with the clinical aspects of early influenza, such as we have outlined it in a previous paragraph, and unless they are thoroughly and critically familiar with the important etiological work that has been done. This alone we would regard as sufficient excuse for an inconclusive summary of etiological studies such as that in the preceding section.

THE EPIDEMIOLOGY OF INFLUENZA

Former epidemics

In diseases like smallpox, diphtheria, scarlet fever, etc., in which sharp clinical and etiological definition is possible, epidemiological data can be obtained with considerable accuracy. In influenza such studies are rendered incomparably more difficult because of the diagnostic difficulties emphasized in preceding sections, and because of the complete lack of any etiological criterion of recognition. During periods of epidemic and especially during the initial stages of outbreaks, the diagnosis of the disease can be established with a considerable degree of certainty. But the widespread catarrhal infections of many different causations, which accompany such epidemics and bring about generalized opportunities for interchange of respiratory organisms, lead to an increased morbidity in which many factors besides the influenzal ones are involved.

Particularly confusing are the problems of recognition in the interepidemic periods during which physicians are forced to use the terms "influenza" and "grippe" upon vague clinical grounds, fully conscious of the diagnostic uncertainty which such a terminology

entails. As we shall see, epidemiologists have been forced for these reasons to base many of their calculations upon atypical fluctuations in seasonal curves of the morbidity and the mortality of the common accompaniments and consequences of influenza, bronchitis and pneumonia.

During widespread epidemics, however, the suddenness of onset, the singular rapidity of rise and fall in each locality, the speed of travel and the general basic similarity of cases and complications, have served to characterize the outbreaks themselves sufficiently to permit their recognition as true influenza. In spite of the uncertainty of diagnosis, therefore, information of considerable reliability concerning the epidemiological history of this disease is available in the writings of past centuries, such as those of Calenus of Greifswald (1579), Jacques Pons of Lyon (1596), Sydenham, (1675), Slevogt (Jena, 1712), Haygarth and Hamilton (1775), Pringle and Huxham, Massin (Strassburg, 1858) and many others. The history of influenza has been dealt with by a number of writers to whose extensive monographs the reader is referred.

Both Thompson and Leichtenstern tabulate the sequence of great influenza epidemics somewhat as follows:

1510—Epidemic, spreading from Malta to Sicily, Spain and all of Europe.

1557—Asia, Constantinople to Europe and America.

1580—First great pandemic. Origin in Orient—to Europe and entire world.

For the seventeenth century the records are very incomplete, but Leichtenstern speaks of an epidemic in North America in 1647.

Less extensive outbreaks seem to have prevailed in different parts of the world between 1709 and 1712.

Between 1729 and 1733 the disease, travelling from Russia westward, spread over Europe in two great waves, one in 1729, the other in 1732.

Another epidemic started on the shores of the Baltic in 1742.

In 1757–1758, 1761–1762, and 1767, epidemics occurred of which we have but poor geographical records.

Of the epidemic of 1742, Friedrich states that all but about one-tenth of the entire population of Germany was attacked.

From 1781 to 1782, an epidemic supposed to have started in China spread through Siberia to Russia and thence to Europe.

Another travelled approximately the same route in 1788.

The same thing occurred between 1799 and 1803.

In 1827, there was an outbreak of Europe less extensive than most of the others.

Between 1830 and 1833 there were two or three pandemic waves, the first one supposedly originating in China.

Other outbreaks, again travelling from East to West, occurred in 1836 and in 1847. During this last named epidemic the Prussian army is said by Friedrich to have been attacked in its entire personnel.

These brief data, which bring us up to the pandemic of 1889, are condensed chiefly from Leichtenstern, who summarizes the general characteristics of influenza epidemics as follows:

1. True pandemic waves.
2. Origin in a specific part of the world. Asia (Netter); China (Pearson); Hirsch believes that some of the epidemics have probably started in North America.
3. Speed of travel over the globe.
4. Sudden mass infection.
5. Rapid burning out after several weeks in one locality.
6. Independence of season or weather.
7. Enormous morbidity with slight mortality.
8. Little influence of age, sex, or occupation on morbidity.

The degree to which these criteria may still be accepted as accurate will appear below.

When we study the records left to us by physicians who described the disease as it occurred in the early epidemics we find close coincidence with observations made during the last outbreak, not only as to the clinical data, but in regard to the chief epidemiological characteristics as well.

Huxham of Plymouth (1743) writes: "About this time a disease invaded these parts which was the most completely epidemic of any I remember to have met with; not a house was free from it. . . . . Scarce a person escaping either in town or country; old and young, strong and infirm shared the same fate." He described the disease almost exactly as we ourselves observed it at Chaumont and Baccarat

in France in May 1918, its sudden onset, fever, chilliness, pains and rapid deferescence in about four days.

These and many other physicians recognized the essentially secondary nature of the serious pulmonary complications.

The pandemic of 1889 is supposed to have originated in the East, though records are available of the existence of an independent focus in Greenland almost synchronous with the observation of early cases in Russia and Siberia. Heyfelder saw cases in Bokhara in May 1889, and traced the enormous speed of travel of the disease north-westward into Siberia and European Russia. By October, it had reached Petrograd, by November it had entered Germany. Rapidly sweeping Westward and Southward it reached France and Austria, Italy and Spain, during this month and December. By the middle of December it had reached London and New York. Its early appearance in New York suggested to some observers the possibility that the epidemic had travelled Eastward from its original focus as well as Westward, encircling the globe, and appearing on our Atlantic coast at about the same time at which it reached the Atlantic coasts of Europe. Its course could be traced by railroad and steamship routes. The percentages of the populations attacked in each country were enormous.

To some extent the speed of travel of influenza can be seen in this epidemic to have increased in the course of the centuries, proportionately with the increased facilities for communication. Thus, in the 1872 epidemic, it took the disease eighteen days to reach Amsterdam from Leipzig, a time which corresponded to the time it took Dutch merchants to reach home from the former place (Leichtenstern).

Transmission

The suddenness of onset of influenza epidemics and the almost simultaneous affliction of a considerable percentage of a community, was perhaps the chief reason for the older beliefs that influenza may be conveyed by means other than contact; and in the past the idea that it was air borne or conveyed by dust and perhaps by insects, has had many adherents. The careful epidemiological studies which were made during the 1889 epidemic and, more recently, during the last pandemic, indicate with considerable certainty that these older

beliefs are not tenable, and that at least the chief means of conveyance is direct and indirect contact with other human beings. The disease does not travel more rapidly than human communication, a belief formerly held. This point was studied with particular thoroughness by observers during the '89 epidemic, more especially by Parsons, Friedrich, Leichtenstern and Teissier. Numerous examples can be cited in which communities that were out of touch with the main population of a country, because of geographical isolation, were spared, or did not begin to develop cases until the reopening of routes of travel. It was noticed, by German observers particularly, that places along the railroad were the first to be affected, while the outlying country with which communication was more difficult, was several weeks late in developing the disease. Often the epidemic would reach points considerably farther away from the places of distribution if they were on main routes of travel, than it would the immediately surrounding but less accessible country districts. This was true of Kiel, one of the earliest of the German cities to be invaded. Extension to distant cities was rapid, while the country surrounding Kiel itself did not begin to report any considerable number of cases until two months later. And even as country districts were reached more slowly than were the centers through which main routes of travel passed, so also did the epidemics percolate through them more slowly and remain in them for relatively longer periods, proportionate probably to the greater dispersion of the population and the lessened opportunities for contact. Thus, Parsons noted that in some of the rural communities of England the epidemic trailed along for some four months during which it swept over the crowded industrial districts with the sudden blazing and subsidence of burning straw.

In large cities the epidemic has usually burnt itself out in a relatively short time. Leichtenstern who has carefully gone over most of the reported data of the 1889 epidemic, generalized in the following way: The first cases are usually followed within two weeks by true epidemic prevalence. After that a very rapid extension occurs which is at its peak in three weeks, and subsides almost completely within the following fourteen to twenty-one days. In Munich, a city which was very carefully studied, the epidemic began about the first of December and from December 27 to January 4 there were 1100 to 1600 cases daily.

By the middle of February the epidemic was almost over. Abbott's careful study of the epidemic in Massachusetts shows that about seven to eight weeks covered the first epidemic period. It reached its peak throughout the State of Massachusetts during the week of January 4 to 11, 1890, and was practically over by February 10. During this brief period over 800,000 people were attacked, that is about 40 per cent of the population. In London the epidemic appeared first in December, 1889, and during January attained a death rate of 28.1 per 1000. During February it rapidly declined and ended during March. It is interesting to note that in some of the large industrial cities of England the epidemic was three to four weeks later than in London, the death rate in London in January not being equalled by most of these towns until February.

During this epidemic also there were a number of more or less isolated communities which were spared. Thus, there was no influenza on the Isle of Man and in the Bahamas. On the Santis Mountain which is about 7000 feet high there was no contact between the inhabitants of the observatory and the valley and there were no cases of influenza during the epidemic. On the Island of Borkum, Leichtenstern states, there was a period of freezing weather in late December and early January, during which the Island was completely isolated. The first cases did not appear until three days after arrival of the first ship. He adds that similar conditions prevailed at Vladivostok and Sachalin, places in which the disease did not appear until the spring of 1890 when the thaws made the resumption of travel possible. Friedrich cites definite data to show that the disease was brought from Danzig to Hadersleben by ship. In France the same thing was observed, and there seems to be very little doubt about the fact that human communication lies at the bottom of transmission from place to place.

During the pandemic of 1918 the same thing was probably true, but because of the active transportation of large masses of men incident to the state of war, the routes of transmission were so completely interwoven that it has not been easy to unravel them. Whether the epidemic spread from France to the United States as suggested by MacNeal, whether it travelled the other way, of whether it began in several places at the same time, are questions that prob-

ably will not be settled until more complete data have been collected by epidemiologists throughout the entire world and have been scrutinized by men as well versed in epidemiological analyses as Frost and others. There is, however, a very interesting example of travel by ship during this epidemic, reported by Colonel Delaney of the American army from England which we cite from MacNeal's paper. On August 26 and 27, a British vessel, the Mantua, with influenza on board, stopped at Sierra Leone for consultation with two British ships, the Chepstow Castle and the Tahiti, the Chepstow Castle acting as a transport for New Zealand troops, the Tahiti carrying navy ratings from East Africa. Influenza appeared on board both of these ships forty-eight hours after this call, with sixty-eight deaths on the Tahiti and thirty-eight deaths on the Chepstow Castle before arrival in port. New Zealand and East Africa had not been reached by the epidemic when these boats started. But on October 23 the steamer Mozambique arrived at Lisbon from Cape Town with 200 deaths during the voyage, and reported an epidemic of influenza at Cape Town at the time it left. Writing in the Lancet (1918, ii, 455) the Medical Officer of Health in India states as his opinion that the epidemic appeared in India with such terrible consequences in the summer of 1918 was not endemic, but was introduced by shipping.

The opinion of direct and indirect transmission from man to man is also well supported by a detailed study of the epidemiology of individual outbreaks. In our own experience with local epidemics such as those at Chaumont, Baccarat and other places, the suddenness with which the malady attacked large numbers of people at almost one and the same time, caused us at first to be exceedingly skeptical of accepting transmission by contact as the only means of conveyance. We considered food and insect transmission as possibilities, and tried our best to find grounds for involving such agencies. But in every case we were forced to return to the conclusion that direct and indirect contact between men came nearest to doing justice to all observed facts.

An interesting small hospital outbreak has been described by Foster and Cookson which clearly exemplifies contact infection. A surgical ward, free from medical illness for some time before, on June 6 received an influenza convalescent suffering from a surgical lesion.

This man spit a great deal, and was dirty in his habits. On June 9 the man in the bed next to him developed influenza and the blood culture of this case contained influenza bacilli (!). On the same day the man on the other side of the original case developed a temperature of 104° with symptoms of influenza but negative bacteriological findings. The disease then travelled from bed to bed, along the line of beds on that side of the ward, until it stopped at both ends when it came to empty beds. Another influenza case was admitted to the other side of the ward, and from it the neighboring bed was infected. But on this side the disease remained limited to these two because the adjoining beds were screened from them by elaborate surgical traction arrangements. The diagram of this little epidemic is sufficiently instructive to warrant reproduction.

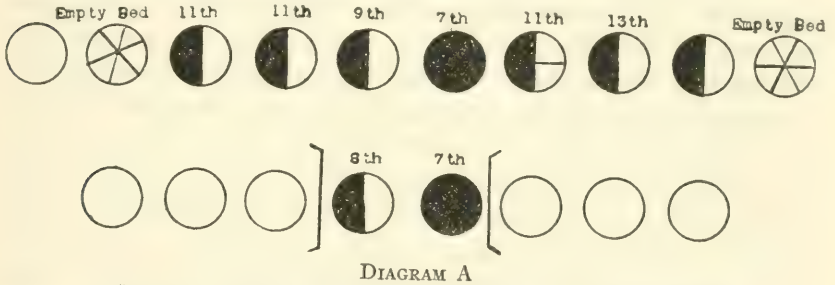

DIAGRAM A
(Taken from article by Foster and Cookson, Lancet, 1918, 2, 585)

Bearing upon the same point are certain data which we take from a report of Stanley concerning an epidemic in the St. Quentin Prison, California. Stanley definitely traced the origin of this epidemic to the admission of a prisoner from the county jail in Los Angeles. The man had been sick before he came in with symptoms described accurately as influenza. On his entrance to the prison he mingled with 1900 men congregated in the ward, and ate in the general mess with them. At night he was locked in the receiving room with 20 other prisoners. On the day following this he had an apparent relapse of his influenza, and was admitted to the hospital with a temperature of 101°, chilliness, pains in the back and bones. Following this an epidemic of unusual severity started in the hospital, reaching its height ten days after the new prisoner had been admitted. On the tenth and eleventh day after the arrival of this man, 1900 or one-half

of the entire prison population were ill. The ordinary daily sick-call of the prison was about 150 to 200, whereas, on these days 700 to 750 appeared at the doctor's office. Stanley also noticed that during the period of the epidemic, which lasted a little over a month, the largest number of cases occurred on the Tuesdays and Wednesdays of the second and third weeks, and explains this by the fact that on every Sunday morning two moving picture shows were given, one at 8:00 a.m. and the other at 10:00 a.m., respectively, in a poorly ventilated room. Almost the entire 1900 sick men had attended these shows. Stanley places the incubation period, accordingly, at about thirty-six to sixty hours. (This corresponds roughly to our own observations in which several cases in which the time of contact could be reliably ascertained showed incubation periods of about forty-eight hours.) About six months after the first epidemic, a second one broke out in the prison, again introduced by a new arrival from Los Angeles. This prisoner became ill on the day after admission, showing the characteristic symptoms. Before becoming ill, however, he had spent one night in the receiving ward, and had taken his meals with the 1900 other prisoners. This epidemic went through the prison more slowly, and there were fewer cases than in the first epidemic. How much this may have been due to immunity of the remaining prisoners, we will discuss further below. In part, the lessened morbidity may have depended upon the very rigid precautions which were taken, the prevention of assembly of prisoners in large numbers, and other sanitary and hygienic measures which were enforced. A third epidemic occurred a month after the second, but lasted only about nine days. During this outbreak a number of interesting additional observations were made. A prisoner, "A," reached the St. Quentin Prison by train on November 21 from Colusa County where an epidemic was then raging. He felt badly the next day, but did not report to the doctor and was put in a room with twelve other prisoners. Though feeling sick he attended the moving picture show on Sunday, on the evening of which day he was removed to the hospital. In the receiving room "B" and "C" slept in adjoining beds. "A" sneezed and coughed into "B's" face at about 4:00 p.m. Sunday afternoon. At 9 a.m. on Tuesday, "B" began to have chills and fever. "C" was also closely associated with "A" and "B," and

became sick on the same day that "B" did. Stanley made a careful study of the distribution of cases in the auditorium where the moving picture shows were held, and found that there were approximately five centers about which the infected men sat; the largest one was in the middle of the room, and in each corner there was a separate focus. Nobody was infected in the orchestra pit, where there were 10 men. The orchestra sat 9 feet in front of the first row of auditorium seats. There was a women's department of this prison which had, at the time, 30 inmates. This is a separate building, and absolutely without contact with the men. None of these women had influenza during the three epidemics. Stanley's studies seem to indicate not only that contact is the method by which the disease is conveyed, but also, that fairly close contact is necessary; and his results show that complete isolation, when it can be rigidly carried out, as in closed institutions, is effective.

Jordan has carefully studied three groups in Chicago, namely, the Students' Army Training Corps, the high and elementary schools of the University of Chicago, and the Chicago Telephone Company. In the Students' Army Training Corps there were two sections, A and B. They lived under the same conditions, but most of the boys in section B came from small towns in Illinois, while most of the boys in section A came from Chicago itself. For some reason or other, section A was closely supervised, with prompt removal of those who were slightly ill, whereas in section B these precautions were not carried out to the same degree, and 3 of these boys were ill on arrival in Chicago. Section A had 26 cases, whereas section B had 92 cases within six days. In the elementary school group Jordan's analyses show definitely that there was a sharp rise about November 30 following the Thanksgiving recess from Wednesday until Monday, during the family gatherings, etc., formed an opportunity for infection, and at which none of the precautions were probably taken which were habitual at this time in the routine of school attendance.

Onset of epidemics of influenza

In regard to the suddenness with which the disease attacks large numbers of people in one and the same place, at almost the same time, recent records thoroughly confirm the observations of the past. In

our own experience during the first outbreak at Chaumont, 54 men of a single company were attacked within 11 days, out of a total strength of 172, and no less than 41 of these 54 men were taken ill within two days, May 15 and May 16. Thus:

On May 13 there were 3 cases
On May 14 there were 3 cases
On May 15 there were 19 cases
On May 16 there were 22 cases
On May 17 there were 3 cases

From then on until May 23 when the disease stopped in this unit, there were only 4 additional cases.

In another place we saw as many as 73 cases, developing in the same day in a single infantry company. Wirgman writing in 1918 speaks of an outbreak at a camp of 560 men in which almost the same sort of thing happened. In a report on an epidemic in Rest Camp no. 4, Base Section no. 2, American Expeditionary Forces, near Bordeaux, Ward reports that in one camp with a strength of 3400 men there were 82 cases within two days, and in a camp of 180 men, there were 20 cases on one day.

Therefore, although the total morbidity and mortality statistics of any influenza epidemic compiled for a large territory usually covers periods of months, yet when the individual local outbreaks are studied, it is found that in any given locality the disease burns itself out within an extremely short time, then passing on to the next.

The speed of travel in influenza may to a certain extent be explained by the almost universal susceptibility of the race to this disease, and to the fact that a large percentage of the cases (especially the early ones) are extremely mild. The percentage of the recognized sick, who seek medical advice does not represent the total number of the afflicted since a very large number of people during such epidemics suffer from perhaps nothing more than headache, general malaise, and trifling fever of short duration. In a military unit which we had occasion to study, we were able to determine that although the number who came to sick call and needed hospital care was very large, there were, in addition to this, a considerable number of men who were unquestionably infected, but who were so slightly ill that they continued on duty. It is not at all unlikely that during epidemics

(and this is a thought also expressed in connection with the '89 epidemic by Leichtenstern) a large number of people are well enough to travel and to go about their daily business, although in the active stages of mild attacks and, therefore, capable of transmitting the infection. In most other infectious diseases the majority of the sick are immobilized, at least for a time, and transmission by travel is thus prevented in the majority of cases.

The free circulation of large numbers of people who represent unrecognized, potential sources of infection, and their unrestricted intercourse with others in all the activities of business life, family relations and travel, coupled with an almost universal susceptibility of the population at times preceding epidemics, would go far to explain both the tempestuous beginnings and the rapidity of extension.

Moreover, as regards the suddenness with which a large number of people are simultaneously afflicted, a feature which has kept alive some skepticism regarding the contact method of infection, such statements should be made with qualifications. Parsons, in his studies of the epidemic in England in 1889, 1890 and 1891, calls attention to the fact that the rapidity of onset in influenza is not essentially different from that which formerly prevailed in smallpox before the day of universal vaccination. It is probable that, when the disease strikes a community, its explosiveness is actually much less marked than it appears to be from morbidity statistics; and, as Leichtenstern and others have noted, it was usual during the '89 epidemics, that outbreaks were clearly recognized as possessing true epidemic dimensions not earlier than two weeks or more after the first cases had actually occurred, a fact not generally brought out until subsequent studies have been made on the basis of completely available data. Parsons, furthermore, has found evidence which indicates that in many cases in which the onset of a local outbreak was particularly explosive, this could be traced to the assemblage of large crowds in meetings or conventions, during the days just preceding the epidemic. In the small town of St. Davids the outbreak followed a large public meeting. In Eccleshall an epidemic followed two or three days after an Odd Fellows picnic. In Kington in 1891 the outbreak was associated with the May fairs.

During the last pandemic this phenomenon of explosive onset was noticed chiefly in connection with military units where association in closely related groups was one of the exigencies of military life. It was quite evident in at least one of the epidemics which we had occasion to study that the characteristics of the outbreak in the military groups differed in this respect considerably from those prevailing at the same time among the surrounding population. Thus, at Chaumont, while the outbreak among the Marines and in some of the other military units took the form of the steep peak which we have described above, the disease extended more gradually and trailed along more irregularly and for a longer time among the clerical force who were scattered in many different billets and offices. And this was still more noticeable as regards the civilian inhabitants of the town, among whom the percentage morbidity was much lower and was scattered much more widely both as to time and place.

Moreover, even in military units like the Marine Company mentioned above, where the explosiveness seemed extreme and "mysterious," simple analysis removes much of the mystery. If we take this little outbreak as an example we see that 6 recognized cases had occurred on the two days preceding the sudden appearance of 19 cases on a single day. These 6 had been in the incubation stage for at least twenty-four and forty-eight hours previously, and probably did not represent the total of infected men; for it is more than likely that there were a number of others who were not sufficiently ill to report at sick call. If we consider, therefore, that at least 6 and probably more men circulated freely among the remaining 166, and ate and slept in close association with them, we find that the apparent suddenness of the rise in morbidity on the third and fourth days of the outbreak is not out of keeping with the assumption of contact infection. The impression conveyed by the steep graphs of such outbreaks is, therefore, apt to be misleading.

Secondary outbreaks

In the wake of almost all influenza epidemics there have followed secondary outbreaks which are often spoken of as "waves." This has apparently been the case in all the large epidemics of which we

have definite knowledge. Leichtenstern has commented upon it extensively in connection with his study of the '89 epidemic.

After the epidemic of 1729 to 1730 there were secondary waves in 1732 and 1733.

The 1789–1791 outbreak did not become entirely quiescent until a definite secondary wave had followed in 1792.

The 1798 epidemic was followed by one in 1800.

After the outbreak of 1836 to 1837, others followed in 1838 and 1841.

The 1847 to 1848 epidemic was followed by another within a year, and conditions in the world did not return to normal until 1851.

Parsons writing for the British Isles states that there were three definite waves from 1889 to 1892. The first began in the winter of 1889 to 1890. Another occurred in the spring of 1891, a third in the winter of 1891 to 1892. The following chart (page 282) taken from the article by Frost and tabulated by months, from 1887 to 1916 for Massachusetts, from death rates per 100,000 from influenza and from all forms of pneumonia, shows that here, too, the epidemic of 1889 to 1892 developed in three distinct waves, the first one coming to a head in January, 1890, the second in April and May, 1891, and the third in January, 1892. The same thing occurred all over the world, and tabulations of individual cities like New York, New Orleans, Chicago, as well as studies in other parts of the world indicate a similar wave-like repetition.

Brownlee has attempted to find a law of periodicity for the large intervals between pandemics, and the intervals between the separate waves of each outbreak. Since statistical studies of pure uncomplicated influenza alone would for many reasons hardly be accurate enough as a basis for such calculations, Brownlee, Frost and other epidemiologists have reduced the factor of error by making their calculations both from influenza statistics and from total reports of all pneumonias, comparing these with the pneumonia incidence and mortality of interepidemic years. Brownlee has studies the weekly number of deaths for London from 1870 on. He finds the period between influenza outbreaks, between 1889 and 1896, to be about thirty-three weeks. There is no such periodicity in regard to bronchitis and pneumonia in the absence of influenza, and Brownlee concludes that if such periodicity appears after the return of influenza,

TABLE 1

Death rates per 100,000 of population from pneumonia (all forms) and from influenza in Massachusetts, 1887–1916, inclusive

PNEUMONIA

YEAR	TOTAL PER YEAR	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER
1887	138.8	19.5	16.7	1.9	22.6	16.1	7.7	5.5	4.1	5.6	9.0	14.8	15.3
1888	172.7	24.7	25.1	26.4	21.3	16.4	8.0	5.5	4.0	6.2	11.4	9.8	13.9
1889	156.6	17.9	16.3	21.1	19.8	14.9	7.5	5.3	5.2	5.4	10.6	13.2	19.3
1890	180.0	47.8	17.7	17.6	20.1	12.7	8.5	6.2	4.8	5.0	9.4	11.8	18.3
1891	188.5	20.6	16.4	20.6	25.1	23.9	10.1	5.9	4.0	4.0	7.7	13.8	36.4
1892	213.0	61.5	25.2	23.1	21.4	17.0	8.3	5.4	4.2	6.8	8.5	12.5	19.0
1893	225.8	27.3	25.4	28.6	33.1	27.3	11.1	8.0	5.0	6.1	9.8	14.3	31.9
1894	166.0	32.8	19.9	22.7	18.5	14.0	8.5	5.1	5.1	6.8	8.2	11.3	13.6
1895	184.1	19.1	34.4	30.8	20.9	14.4	7.6	5.6	5.3	4.7	10.5	13.4	17.3
1896	182.0	19.5	20.7	24.9	25.9	18.7	10.3	7.6	4.5	7.6	10.7	12.7	18.8
1897	181.6	21.1	24.9	31.5	19.7	15.2	10.2	7.0	4.5	6.0	11.7	13.1	16.9
1898	156.0	18.8	17.1	18.5	18.7	15.7	6.6	6.0	4.8	5.6	10.6	12.8	21.0
1899	181.3	37.5	25.8	20.6	18.4	14.0	8.9	5.0	4.8	5.8	8.2	13.2	19.0
1900	188.3	22.7	21.1	42.0	30.5	17.6	8.7	5.3	4.3	5.3	6.2	9.9	14.7
1901	167.7	22.6	26.6	26.2	19.9	13.9	7.7	3.4	3.4	5.7	9.1	14.2	15.1
1902	158.9	15.7	18.9	19.9	16.8	15.5	8.0	6.2	5.3	5.7	11.8	14.5	20.6
1903	172.5	25.2	25.8	25.4	18.1	16.8	8.2	7.0	4.5	4.6	7.7	13.3	18.9
1904	172.1	22.6	22.7	24.1	21.2	14.2	6.7	5.9	4.4	6.5	9.4	15.0	19.5
1905	178.3	24.7	27.7	23.6	17.1	15.5	8.5	5.4	4.8	6.2	8.9	15.8	20.0
1906	174.1	22.5	21.9	24.1	21.7	14.9	5.1	6.2	5.0	6.0	9.4	13.8	21.0
1907	180.4	25.5	24.4	23.4	18.3	14.3	9.5	5.1	5.1	7.1	9.3	12.7	26.9
1908	165.8	26.6	22.2	21.1	19.4	13.5	6.6	4.9	5.8	6.4	9.2	12.4	17.6
1909	170.3	22.1	20.0	26.1	20.1	16.0	9.7	5.1	5.0	5.4	8.9	13.6	18.3
1910	197.6	24.1	20.7	27.5	23.3	16.9	9.7	7.3	6.3	9.1	12.3	17.0	23.6
1911	174.4	22.6	27.1	23.9	20.2	16.9	7.2	6.7	6.1	6.7	9.0	11.8	16.2
1912	152.0	19.8	20.2	21.2	16.4	13.3	6.2	5.0	4.1	5.8	9.5	10.5	19.9
1913	172.2	23.5	22.8	24.9	19.3	17.1	10.7	6.2	5.4	6.7	8.3	10.4	16.8
1914	166.0	22.9	20.1	23.2	20.4	15.2	8.2	5.1	5.5	6.0	10.1	12.6	16.8
1915	176.0	17.8	19.3	28.5	27.7	13.6	6.6	7.1	5.8	6.0	8.8	9.8	22.1
1916	176.6	35.6	25.5	23.0	17.3	14.0	7.4	5.3	4.1	5.9	7.6	12.8	18.3

Taken from Frost, Public Health Reports, U. S. Public Health Service, xxxiv, no. 33, p. 4.

it must be definitely associated with this disease. From 1876 to 1889 the thirty-three-week recurrence was missed in regard to bronchitis and pneumonia, but in the years 1889 to 1896 it was marked. Comparing the monthly statistics of Glasgow, Aberdeen and Massachusetts he finds that there is nothing which differentiates them in principle from the phenomenon in London. Stallybrass supports these calculations of Brownlee, and speaks of a minor cycle of thirty-three weeks within the pandemic periods and major one of about ten years between pandemics. We are not ourselves in a position to comment upon these findings.

Pearl's paper "Influenza Studies" published in 1919, incidental to an analysis of the mortality curves of 40 American cities takes up the time manifestations as they occur in local outbreaks. He finds that such curves are of two main types, one showing a single well-defined peak, others showing a first high peak followed by one or more smaller ones. The latter type was of the usual form. A further analysis of these curves showed that there was a definite tendency for the "two-peak" curves to fall into two groups. About one-third of them had their second mortality maximum about eight weeks after the first peak. The remaining two-thirds had their second mortality maximum on an average of about thirteen weeks after the first peak. Those in which there was a third peak had their second one about 7.1 weeks after the first, and the third on an average of about 13.1 after the second. Pearl believes that according to this, the cycle in such successive waves appears to be nearer a multiple of seven rather than of ten weeks.

A great many statisticians, far more capable of judging of these matters than ourselves, are now engaged in a study of the cyclic phenomena and no doubt will publish their conclusions in time. Meanwhile, we wish merely to mention the matter as one of the important problems of influenza study undertaken at the present moment.[2]

The second and third waves of epidemics have been marked by a number of characteristics which are of important significance. Both

[2] For a more extensive discussion of the problem of periodicity and its probable significance, we may refer the reader to the extensive monograph of Warren T. Vaughan, published since this paper was first prepared.

Parsons and Frost find that in the epidemic of thirty years ago the mortality was progressively higher during the 1891 to 1892 waves than during the original outbreak in 1889. Leichtenstern states that although the mortality, which of course is largely due to secondary infection, is greater during the secondary waves, the general morbidity of influenza is smaller. This corresponds with the observations of Wutztorff who analyzed the epidemic in Germany with considerable care. Wutztorff admits that it was extremely difficult to obtain accurate estimates of influenza morbidity during the later waves of the pandemic. But, although he finds that in some towns, especially in North Germany, the 1891 to 1892 wave was almost as extensive as that of 1889 to 1890 had been in other places, in general the morbidity in Germany was much lower. To some extent his conclusions are derived from indirect evidence such as, for instance, the fact that the hospitals in the various cities were not taxed to overflowing during these later waves as during the first, massive infection of the entire personnel of many industries and of railroads did not take place to the same extent, and the statistics of the government physicians stationed in various parts of Germany showed that a much lower percentage of the population sought medical advice. As a rule, from 6 to 7 per cent of the population sought treatment during the first epidemic, whereas only from 2 to 3 per cent reported during the later waves. It would be impossible to reproduce the extensive statistical and other evidence brought forth by Wutztorff in support of his contention, but we may assume as probably correct that in the later waves morbidity is usually lower and the percentage mortality somewhat higher than during the first.

Noticeable also is the fact that secondary epidemics do not travel with the same speed and to the same geographical extent as does the first wave. There is generally slower progress, a greater scattering of cases, and a somewhat more prolonged period of prevalence in the subsequent waves; and, judging from the careful study of mortality statistics in years following the pandemics, it is more than likely that after the so-called third wave there may be a succession of what we may term gradually diminishing "ripples" which finally fade out, in the course of some years, into practical quiescence. Leichtenstern seems to believe also that the secondary outbreaks are characterized

by the fact that they originate in many different foci simultaneously instead of proceeding (as he and some others assume that first waves do) from a single focus. Netter holds the same opinion. He says of the secondary waves of the 1889 pandemic that "they have appeared in separate, synchronous or successive explosions, and we have not been able to trace any connection between various reappearances in different places, as this was possible in 1889. There seems to have been an independent reawakening of the epidemic in different localities." In a general way this is probably true, but we will see, when we come to discuss the course of the first wave of the last pandemic that some of the most experienced epidemiologists are reluctant to assume that this outbreak proceeded from any single world focus.

The origin of influenza epidemics with particular reference to the origin and course of the last pandemic outbreak (1918)

In a recent address to the Congress of American Physicians and Surgeons, Flexner made the interesting suggestion that perhaps the most effective method of forestalling epidemics in the future would be to search out and attempt to circumscribe the endemic foci in which the cinders of disease are constantly smouldering during the interepidemic periods. This method of procedure has been effectually initiated in the case of yellow fever, and would seem to be an eminently logical one for application to other insect borne diseases. It might also be successfully applied in plague and conditions like it in which interepidemic propagation is carried on largely in animals. In regard to other diseases the promise of even partial success would be directly dependent upon the question as to whether the particular condition is kept alive, between outbreaks in special centers in the world or whether the foci are widely scattered in all populations in the persons of carriers, constantly increasing in number along the trail of sporadic cases, as in typhoid and the paratyphoid fevers, etc.

The idea is an extremely important one since any step in the direction of interepidemic control of foci, if attended by even a slight degree of partial success, would accomplish more at smaller expense than the most energetic attempts at suppression after epidemics have started. Moreover, the splendid efforts which are being made, at the present time, to internationalize public health activities pro-

vide an opportunity for possible accomplishment of such a project which has never before been within reach.

In the case of no disease should this proposal be more seriously considered than in that of influenza, since no other condition attains a comparable degree of destructiveness, none travels so sweepingly over the whole world, and in none other are we so totally helpless to obstruct its progress. It is, therefore, of great importance to determine, if possible, whether influenza epidemics have truly emanated from definite endemic foci, or whether they have started in various parts of the world at times when conditions such as the declining resistance-values of populations, or some other unknown factors have created epidemic possibilities.

In the tabulation cited from Leichtenstern and others we have indicated that many of the epidemics of the past were supposed to have emanated from the East. Flexner, unquestionably following similar reports, assumes that the region on the border between Russia and Turkestan may possibly be regarded as one of the important endemic foci. At any rate, the reports of earlier writers have again and again referred to China, the Caucasus, Eastern Siberia and Turkestan as furnishing the initial blaze which then spread, Westward and Eastward, to encircle the world. The possibility of the regional delimitation of influenza foci is, therefore, more than a surmise and should be examined with care, especially as light has been thrown upon it by the more exact epidemiological investigations of the last two great outbreaks.

The beginnings of the outbreak of 1889 seemed again to be traceable to the East. The reports of Heyfelder and others to this effect have been mentioned in preceding sections, but there seems to be evidence that the disease appeared in Greenland and in Northern Canada at a time so early in this epidemic that it cannot be accounted for by Northwesterly spread from the South Eastern continental sources.

It appears also from the studies of statisticians that influenza remained widely dispersed throughout the world for many years after this epidemic had subsided; so long in fact that it seems very unlikely that we can ever speak of well defined endemic potential sources of origin except in a relative way. Indeed, the permanently increased influenza incidence in places like China, if considered from this point

of view, may be due to nothing more than to defective conditions of hygiene and sanitation coupled with greater crowding. Prof. Raymond Pearl in commenting upon the probability that the 1918 epidemic will be followed by a long period of increased influenza morbidity, makes the statement that the curve of mortality from influenza in England and Wales was higher in 1907, seventeen years after the 1890 epidemic, than it had been in any of the forty years immediately preceding this outbreak. He adds that a similarly slow decline of mortality followed the epidemic of 1848.

It is likely, therefore, that for many years after pandemic waves have subsided, perhaps throughout the interepidemic periods, the virus remains freely scattered among the populations of the world, ready to flare up in renewed mass infections when gradually declining incidence over a period of years has brought about a reduction of community resistance; and at such times it would be most likely that the points of least resistance, (and, therefore, the most frequent sources of widespread epidemics) should be located in the most crowded and least sanitated communities.

It is too soon to come to any definite conclusions regarding the origins of the 1918 epidemic. Epidemiological methods have developed considerably since the last preceding outbreak, and no final judgment can be rendered until properly qualified epidemiologists have had the opportunity of gathering and studying all available evidence. Like others who cannot pretend to anything more than a superficial knowledge of statistical methods, we must be content to await these analyses. Meanwhile, however, it will be of interest to discuss available information on this problem in a tentative way.

As in the case of previous epidemics this one is supposed by some writers to have originated in the East. McNalty, in the article referred to above, states that in March, 1918, the disease was prevalent in China, and that, in the same month and in April, the Japanese navy, perhaps infected in Chinese ports, suffered from a serious outbreak. This is particularly interesting to us, since we remember distinctly hearing of a curious, mild febrile disease reported among Chinese labor troops on the coast of France early in the spring of 1918, about which we have never been able to obtain definite clinical or epidemiological information. These facts would incline one again to suspect

the existence of a single source of origin. More searching inquiry into the beginnings of this pandemic, however, throws considerable doubt upon such a simple solution of the problem. Frost who has given particular attention to the study of general mortality rates from influenza and pneumonia has, among other things, analyzed these rates for a number of American cities during the years 1910 to 1918. He finds that in December, 1915, and January, 1916, there occurred in New York and Cleveland a sudden and considerable rise in the mortality rates from these diseases. In January, 1916, he states, influenza was reported to be epidemic in twenty-two states of the Union (U. S. Public Health Reports, January 7, 1916)—epidemics which "were so mild that they attracted little attention at the time and were generally forgotten." Even though we make all due allowance for the looseness of the clinical term "influenza" by which many of these cases were reported, these facts are significant in pointing to unusual conditions in regard to the prevalence of diseases of this type some years before the pandemic gathered sufficient velocity to be seriously regarded.

During the winter of 1917, when the army concentration camps were being filled in the United States, pneumonia occurred in many of them in an epidemic form, which, however, was in most cases unassociated with any influenzal element. In a few cases, however, mild influenza-like outbreaks preceded or accompanied these pneumonia epidemics. When recently we described influenza as we first saw it at Chaumont, France, in May, 1918, we were told by Dr. George Draper that he had seen a number of exactly similar cases at Fort Riley in the winter of 1917. For Europe, too, there is evidence that indicates that influenza was endemic during the years preceding the great outbreak and that a number of minor epidemic explosions had occurred in the years just preceding 1918. MacNeal who has investigated military reports, particularly, states that small epidemics occurred in the British Army in 1916 and 1917. A chart constructed by him, from the American Expeditionary Force reports, shows that a considerable rise in reported influenza cases took place in November and December, 1917, and in January, 1918, gradually declining toward spring. MacNeal, compiling the data available in the office of the chief surgeon, American Expeditionary Forces, states that the

influenza morbidity reported per 100,000 for succeeding months in 1917, were as follows:

July	321
August	438
September	404
October	1050
November	1980
December	2480

Robertson who studied many of the secondary pneumonias which came to autopsy at this time found an unusual type of lobular pneumonia in which Pfeiffer bacilli were frequently found. In many of these cases the organisms could be obtained from the nasal sinuses and antra. Similar findings were reported by British bacteriologists (Hammond, Rolland and Shore, Lancet, 1917, ii, 41, and Hallows, Eyre and French, Lancet, 1917, ii, 377) who studied the cases that occurred in the British Armies both at home and in France. We have also found in reports by Austrian physicians reference to outbreaks of typical influenza on the Austro-Russian front early in 1917.

There seems little doubt, therefore, that for some years before the pandemic of 1918 influenza was endemic in many parts both of Europe and of America. As early as 1915–1916, Frost finds evidence of limited epidemic outbreaks in the United States. During the winter immediately preceding the true beginning of the pandemic small outbreaks occurred among the allied troops in France, the British troops in England, and probably among American troops gathered in home concentration camps as well. MacNeal in a summary of the conditions prevailing among American troops in France concludes that epidemic influenza in that country originated from the endemic foci there existing and that the disease was probably carried from Europe to the United States by shipping. The former assumption, namely, that the epidemic occurrence of the disease may have been due to the fact that an enormous and concentrated newly introduced material of susceptibles may have been lighted into flame after arrival in France at the numerous endemic "smoulders," may well be correct. The latter, however, concerning the transportation of the disease from Europe to America may justly be questioned. For, in the first place, Frost's studies have shown that prepandemic outbreaks were quite

as frequent in the United States as in Europe during 1915 and 1916, and, though we have no definite proof of this there is reason to believe that influenza was prevalent in concentration camps during 1917.

Moreover, when the disease was beginning to gather headway in the rise of the first wave in 1918, definite outbreaks in the United States seem to have preceded those in Europe. The earliest reports from Europe, so far available, seem to place the beginnings of the epidemic somewhere in April, 1918. Yet in March there was a very definite though mild epidemic at Oglethorpe, Georgia, which was reported by Vaughan and Palmer and has been referred to above. Similar epidemics seem to have occurred in Chicago in March, and the epidemic which occurred in St. Questin Prison in April was, according to Stanley, started by the reception of an infected prisoner from Los Angeles, where the disease must have been prevalent at that time. It was at about this time that the writer heard of the curious disease among French Indo-Chinese troops on the Coast of France, a matter that is mentioned only in order that some one who may have access to suitable records, may on reading this, look for evidence more definite than rumor. The first concise reports in Europe seem to have come from Spain in May. The course of the epidemic after this time is extremely difficult to follow owing to the concentration of large bodies of men under active military conditions and the transportation of troops from one country to another. Within a month it had spread to Portugal, France, Holland, Germany, Austria, Hungary, Russia, Switzerland, Norway and Denmark. What the exact order of appearance from one country to another may have been, we are not in a position to say. Nor are we sure that it will ever be possible to trace this even when all records are available. Certain it is that outbreaks soon became almost simultaneous in many different parts of the continent. By June it had appeared in the Philippines and India. (In India too there had been mild outbreaks earlier in 1918 in the Province of Tana, presidency of Bombay, but a report from Major White to the government of India indicates that a fresh introduction of the disease seems to have taken place in May when cases were reported in Bombay, subsequent to the arrival of a transport from Mesopotamia.) A little later it spread through South Africa and in July appeared in Egypt whither it is said to have been brought from Malta and Salonica.

It seems fairly definite, therefore, that the last pandemic cannot be said to have started in any single endemic focus. It appears to have grown from roots that can be traced back to 1915 and 1916 at least, and according to studies such as those of Pearl it seems quite possible that none of the crowded communities of the world had become entirely freed from the disease after the 1889 outbreak. It is not impossible, however, that the last pandemic may have been epidemiologically abnormal owing to the unusual conditions incident to war, the creation of great foci of respiratory transmission in the camps and the transportation of infected men in large numbers under conditions eminently suitable for the dissemination of disease. Moreover, there was a constant rearrangement of human association, a constant addition of fuel to the centers of epidemic prevalence, in the form of recruits sent to camps, American susceptibles sent to France and transport-infected individuals unloaded into dense populations in both directions between Europe, America and other continents. It is a suggestion at least worth considering whether this pandemic might not have been delayed in its advent, or perhaps limited in its scope had there not been a state of war throughout the world.

Thus, although the last epidemic unquestionably started from a number of different sources, and although it will probably take many years before the respiratory disease rates have returned to normal interepidemic levels, it will still be eminently worth while to study the problem as to whether there are localities in the East in which, owing to particularly unfavorable sanitary conditions or other factors the disease is more prevalent than in the rest of the world, and to begin prophylactic epidemiology in these places.

Course of the pandemic of 1918

Like the 1889 epidemic the last pandemic appeared in successive waves. It is a little difficult at the present time to say exactly when we should consider the first wave to have started. In the United States the sharp rise of influenza mentioned by Frost as occurring in 1915 to 1916 might be considered a preliminary wave.

According to the report of the surgeon general of the United States for 1918, it is not impossible that a definite influenza epidemic existed in the United States in 1917. During this year he states that approx-

imately 4572 cases of influenza were reported in the United States army, but no separate tabulations by camps were made at that time for the Annual Report. Practically none of the 1917 cases were reported as associated with pneumonia, but in analyzing his tabulations the surgeon general concludes that in a large number of the camps in the United States in 1917 there were epidemics of influenza which began in October, extending through November, usually decreasing in December, with further decrease in January, decided decrease in February, and a subsequent increase either in March or April. Furthermore. a number of cases of the disease were reported during the summer months together with a considerable number of pneumonias. The surgeon general also notes that from the very beginning of 1918 there was a respiratory disease rate above normal.

A similar early appearance of the disease in 1917 in minor outbreaks in the British army and in France generally has been alluded to above in the attempt to analyze the possible origins of the last pandemic. When the history of the epidemic is finally written by competent statisticians on the basis of accurate data it may well be found that it did not appear in its maximum force in a first overwhelming wave, but that there was a gradual sequence of progressively increasing wavelets which led up to the main outbreak, analogous in a reverse way to the gradual decline in waves as the epidemic subsided; and, although, this seems quite different from the story of past epidemics, it is not impossible that this is due only to the fact that in earlier epidemics the preliminary outbreaks were insufficiently recognized and studied. Thus, we have already noted above that Heyfelder speaks of the similarity of his early cases in 1889 to cases of so-called dengue fever which occurred in Constantinople in 1888.

However this may be, the first generally recognized wave of the last pandemic seems to have occurred in the spring of 1918. This probably began in March, April and May, at which time there were reports emanating from China and Japan almost simultaneous with similar reports from Camp Oglethorpe in America, followed rapidly by outbreaks in France among civilians and American, French and British troops. It seems at that time to have been prevalent in American cities, especially New York and Chicago, appearing in Spain in the latter part of May and early June, reaching England in

June and July. According to the information we can gather from the German medical press, the disease must have been prevalent in Germany and Austria prior to July, 1918. At probably the same time it reached South Africa. According to a report of Major Norman White, high sanitary commissioner of India, the disease began epidemically at Bombay in June, 1918, but the first sporadic cases seem to have occurred in May on a troop ship coming from Mesopotamia which indicates that the disease must have been in Mesopotamia previous to that. According to Findlay the first cases in Egypt occurred at Port Said in the middle of July, introduced by shipping from Malta and Salonica.

According to Frost the rise in the Central and Western cities of the United States occurred in April when the pneumonia reported showed an unmistakable departure from the normal; and the increased mortality extended into May. But Frost notes that on the Atlantic seaboard, especially in New York there was a definite increase generally during the January, February and March, preceding.

It seems definite then that the first well defined wave of this epidemic started in different parts of the world between the months of January and June, 1918, the largest number of outbreaks taking place finally about the middle of June.

There is no complete interval of freedom between the first and second waves, a thing which we are inclined to believe probably never occurs, but the first wave declined very susceptibly.

By September and early October, the second wave which was the really destructive one in this epidemic, had gathered its full velocity. In the United States it came at that time with such sudden force that it appeared as the first onset of the epidemic, the importance from an epidemiological point of view of the earlier outbreak mentioned above not being generally appreciated at the time. The following chart taken from the article on the epidemiology of influenza by Frost which has been repeatedly quoted above, illustrates the manner in which the outbreak appeared in Boston, Washington, and San Francisco. Events identical in principle occurred in Philadelphia and New York, beginning at about the same time. The New York curve was, however, much less extensive than that which occurred in Philadelphia at this time, and the curve as charted by Frost for

St. Louis is a little later in advent, did not reach its maximum until the middle of December and was much less high than either of the others. This wave seems to have affected the entire world, and before the end of October had swept over Russia, China, South Africa, and parts of South America.

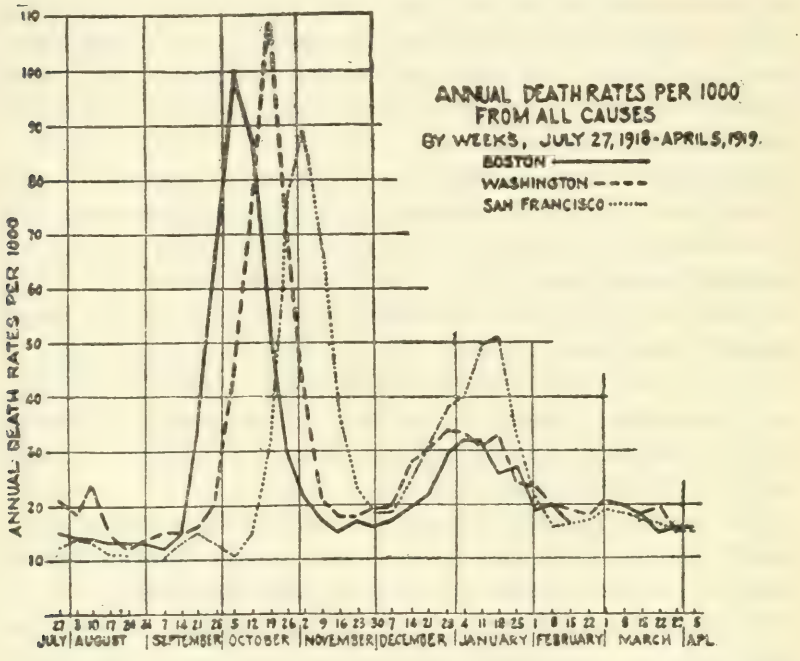

Chart taken from article by W. H. Frost, The Epidemiology of Influenza, U. S. Public Health Reports, August 15, 1919, no. 550, p. 1823–1836.

The second wave was also present in India, reaching its greatest intensity in the central, northern and western parts of the Indian Empire. The greatest number of deaths in India seem to have occurred in October and November, and by November was on the decline in all parts of India. By the end of the month, mortality had become almost normal. In Great Britain the second wave appears to have begun a little later than in America, according to McNalty beginning in October, reaching its maximum in the last week of

October, and lasting about three or four weeks. By the end of December it had practically ceased.

A third wave followed almost immediately upon the second in many parts of the world, in Great Britain appearing so soon after the decline of the second that there was hardly any interval. It began approximately in the latter part of January, reached its height in the middle of February and had come down to almost normal by the beginning of April.

Another rise took place in America also in the month of January during which over 50,000 cases were reported from 17 states for one week, over 59,000 in the following week.

It is not our intention to attempt a statistical tabulation of the epidemic throughout the world at this time, further than to indicate that three very distinct waves occurred in rapid succession in most parts of the world in which epidemic studies were made. But this did not by any means end the history of this epidemic. In the fall of 1919 and the beginning of the year 1920, a very distinct rise of influenza cases again occurred in the United States. A general increase of cases as reported to the United States Public Health Service from the various state and city officers of public health is indicated in the tabulations of early January of this year which grew materially larger in February and declined in March. It is more than likely that recrudescences will continue to occur for some time, especially in crowded centers.

The mortality in the second wave was enormous. Pearl estimates that in the United States alone, the deaths from the influenza epidemic were not less than 550,000, "which is approximately five times the number (111,179) of American soldiers officially stated to have lost their lives from all causes in the war." A fair index of the severity of the epidemic can be gathered from the surgeon general's report. Influenza together with its complications is charged in this report with over 600,000 admissions of American and native troops for the year 1918. The total rate was 273.52. It caused 23,007 deaths. If to these are added deaths from bronchitis bronchopneumonia, lobar pneumonia, and other conditions probably secondary to influenza, the total number of deaths would be 39,371. Approximately 82 per cent of all the deaths could be attributed to acute respiratory

diseases. An idea of the death rate in India as taken from the report of Major Norman White (Bulletin of International office of Public Hygiene, Paris, May, 1919, p. 471–490) can be gathered from the attached table taken from this report as quoted by the United States Public Health Service.

PROVINCE	POPULATION (CENSUS OF 1911)	ESTIMATED NUMBER OF DEATHS FROM INFLUENZA	INFLUENZA DEATHS PER 1000 POPULATION
Ajmere-Merwara	501,395	33,407	66.6
Central Provinces and Berar	13,916,308	790,820	56.8
Delhi	416,656	23,175	55.6
Bombay	19,587,383	900,000	45.9
Punjab	19,337,146	816,317	42.2
Northwestern Frontier	2,041,077	82,000	40.0
United Provinces	46,820,506	1,072,671	22.9
Coorg	174,976	3,382	19.0
Madras	40,005,735	509,667	12.7
Assam	6,051,507	69,113	11.4
Bihar and Orissa	34,489,846	359,482	10.3
Burma	9,885,853	60,000	6.0
Bengal	45,329,247	213,098	4.7
Total for British India	238,527,635	4,933,132	20.7

Table taken from Report of Major Norman White, Bulletin of the International Office of Public Hygiene, Paris, May, 1919, p. 471–490.

The problem of immunity in influenza and its epidemiological significance

The explanation of the peculiar phenomenon of successively fading waves, of course, suggests the gradual development of immunity. This would be the simplest explanation and the one on the basis of which we could reason with some clearness. The question, therefore, of whether an individual and, therefore, a community as a whole develops immunity upon an attack of influenza has been the subject of many inquiries. To base any opinion upon the numerous reports of second attacks in individuals would be entirely misleading. The writer himself believes that he had three attacks during the last pandemic; the first and second mild ones, and the third complicated and, therefore, severe; and innumerable others with whom he has spoken have had similar experiences. But, although such observa-

tions indicate with great definiteness that any immunity resulting from an attack of influenza can be a relative one only, and far less protective than the immunity conveyed by an attack of typhoid fever, smallpox, etc., a judgment of the problem as a whole can be obtained only by statistical studies of large numbers of people during the secondary waves. For even a very limited immunity might be sufficient to prevent infection in a majority of people who, in the ordinary course of association with others, are subjected to very indirect contact with minute doses of a virus which has often attenuated by conditions outside the body; and this might be sufficient to determine the difference between true epidemic prevalence and a limited, sporadic sick rate.

It is a fact that Germany and France were spared to a great extent in the spring of 1891 when North America and England suffered more severely. Parsons believes that his studies have shown definitely that there is a transitory state of resistance in a population that has been thoroughly permeated by the first wave. In his analysis in England he found that a number of communities that had suffered severely during the early epidemics were afflicted but slightly during the second, and vice versa. At Winton near Manchester at a boys' school there was a serious outbreak in March, 1890, during which 171 out of 589 children came down with the disease. In 1891, this school had almost the same inmates, 449 of the children in attendance at that time having been there throughout the earlier epidemic. In 1891, there were only 25 cases; and only 4 of the 150 who had had the disease in 1890 had it again in 1891. Two hundred and ninety-nine, who did not get the disease during the first epidemic, although thoroughly exposed, were perhaps insusceptible, since only 17 of these came down during the second wave. Conversely, a town on the Tye which escaped lightly during the first two waves, suffered heavily during the third. In Brighton there was a low death-rate during the first epidemic, and a higher one during the second and third waves; similar facts are cited for Portsmouth and Plymouth. In the St. Quentin prison epidemic which we have mentioned above, Stanley states that the second epidemic was less severe than the first, and the third far less severe than the second and, in analyzing these facts further, he finds that the men who entered prison after the first

epidemic had subsided, were attacked in greater numbers than those that had been there before, although there were more of the latter than the former. Frost has studied immunity conditions during the last epidemic, a matter that is still fraught with great difficulties because of the incompleteness of records of the second and third waves at the present time. He made a canvass of many thousands of people in Baltimore between November 20 and December 11, 1918, and a second inquiry during January among 320,600 people; 724 cases of influenza were found to have occurred since his first survey. Of these only 26 were confirmed by reliable methods as having been true second attacks, and in not all of these was the diagnosis absolutely definite. He states that in view of the fact that "23 per cent of the population had had influenza previous to December 11, the proportion of second attacks should have been very much greater if no immunity had been acquired." Warren T. Vaughan has made an excellent and extensive analysis of the literature on this question in which he has collected a considerable number of reports which point in the same direction as the studies of Parsons and of Frost quoted above. Thus, the observations of Lemiere and Raymond, of Gibon, of Dopter, of Opie, Barthelemy, of Hamilton and Lennard, of Niven and others, all indicate that influenza leaves the individual and, therefore, the community through which it has swept, relatively more resistant than normal for a limited period. This period is appraised by Warren T. Vaughan as not shorter than three months, the acquired resistance gradually and rapidly fading thereafter. Such a conception would explain the apparently contradictory results of Jordan and Sharp, and of some observations of Frost, courteously placed at our disposal by him in a letter dated June 18, 1920. In a recent paper (Journal of Infectious Diseases, May, 1920, p. 463) Jordan and Sharp have analyzed the incidence of influenza, in subsequent waves, at the Great Lakes Training Station and at Camp Grant at Rockford, Illinois. In each of these places they divided the men into groups of those attacked and those not attacked in 1918–1919, and compared the incidence among these two groups with the respective incidence in January, 1920. Their results indicate that no marked immunity exists twelve to fifteen months after its attack. Frost states that, "in Baltimore those persons who were attacked during the 1918 to

1919 epidemic showed no relative immunity during the epidemic of 1920." This is not therefore in contradiction to the earlier Baltimore studies cited above, since in that case the interval between the epidemic waves was not more than about three months.

It thus appears that, as far as we can gather from careful studies of many workers in different parts of the world, a definite increase of resistance if left behind after an attack of influenza which, though insufficient to protect all individuals, is still adequate to leave the community in a condition of relatively high resistance for a limited period. This period is variously estimated as approximately three or four months, and is certainly less than one or two years.

The bearing of such an immunity upon periodicity and wave-like curves of influenza epidemics is obvious.

The problem of the fluctuation of virulence of the virus

In the analysis of the conditions which govern the rise, fall and disappearance of epidemics, however, account must be taken of another influence, the reciprocal of the immunity factor, namely, the possible fluctuations in the virulence of the causative agent. It is perfectly clear to every one who has studied epidemics that the development of immunity alone cannot satisfactorily explain many of the peculiar manifestations of the outbreaks. Thus, even in epidemics in which the disease leaves behind a permanent immunity and in which, therefore, survivors represent an ever increasing non-susceptible bulwark of transfer between the infected and the susceptible populations, the decline of epidemics is not often a simple downward curve, and the mortality percentage declines with the morbidity. This last fact we have noticed particularly in typhus epidemics where, in the Serbian one for instance, a death rate of 50 or more per cent at the height of the outbreak declined to between 15 and 20 per cent as the morbidity became less. There are many other observations which would incline one to assume the manifestations and the general course of a prolonged epidemic are influenced as much by changes on the part of the infecting factor as they are by the acquisition of generally increased resistance.

The analysis of this problem is not an easy one. On the one hand, we know from laboratory experimentation that, in general, it is pos-

sible to enhance the virulence of a race of microörganisms for a given species of animals by successive passages through such animals, avoiding intervening cultivation on artificial media; this, of course, provided that the organism in the first place renders the animals severely sick, or kills them. Thus, passing a pneumococcus or streptococcus from mouse to mouse, directly from the peritoneal exudate or heart's blood, will, with many races (though not with all races of streptococci) result in a considerable increase of infective power. Even a short sojourn on artificial media, interrupting this serial transmission, will definitely reduce infectiousness in many cases, as has been shown most clearly perhaps by the Barber method with anthrax bacilli. Passage through one species of animal may reduce or increase virulence for other species, according to the particular germ and animal species used, but this has no direct epidemiological bearing. Thus, it is not unlikely that as an epidemic spreads rapidly, a tremendous enhancement in the virulence of the germ may follow and the morbidity, as well as mortality increase rapidly. Such an enhancement of virulence by rapid transmission directly from man to man is entirely analogous to repeated animal passage, and as an excellent epidemiological example of such a case, Warren Vaughan cites the havoc played by streptococcus hemolyticus in American army camps after it had been disseminated for some time as a secondary invader of measles, subsequently acquiring virulence which enabled it to become an independent etiological agent or a fatal primary respiratory disease.

Such an enhancement of virulence, however, will rapidly reach a maximum and at the time when this maximum is reached, the general resistance of the surviving community will probably have attained a level somewhat above normal. In a disease like influenza where initial susceptibility is general and mortality of the pure, uncomplicated disease is low, this increase of resistance on the part of the community may almost keep pace with the increased virulence of the organism, and under ordinary conditions the initial wave will subside when fewer and fewer of the individuals infected with the now fully virulent virus are normally susceptible.

The conditions now established are those of the approximation of a balance between virulence of infectious agent and resistance of the

community which balance, however, is never perfectly established and, therefore, numerous individuals of relatively low resistance or who have escaped sufficient contact during the earlier period of the epidemic, are still afflicted with the disease, and among these we may assume that an increasing proportion have attained a resistance somewhat greater than normal, if not sufficient to protect completely, and this element may contribute to the lessened mortality which accompanies the declining morbidity.

At this point another well known biological principle may be introduced, a principle which has been most clearly and thoroughly discussed by Theobald Smith. Theobald Smith speaks of highly pathogenic organisms as "incompletely adapted parasites." "The less complete the adaptation to the host, the more violent the disease produced." Thus, the acuteness of an infectious disease is an evidence of the tempestuous manner in which the host is trying to rid himself of the invader, a struggle in which the bacteria develop the defenses of capsule, etc., and the offensive weapons of poison formation and perhaps rapid multiplication. As long as this reaction on the part of the bacteria carries the upper hand the increase in virulence will continue. Conversely, however, as Theobald Smith points out, indeed, has long pointed out in some of his former papers, the chronicity of a disease is largely dependent upon an adaptation between host and invader in which the reaction to the parasite is less violent, and a condition approaching more and more closely to a sort of symbiosis, is established. As Theobald Smith puts it in a recent paper which is also quoted by Vaughan "there is a struggle on the part of the parasites to adapt themselves and to establish some equilibrium between themselves and their host;" again, "the final outcome is a harmless parasitism or some disease of little or no fatality unless other parasites complicate the invasion."

Such adaptation unquestionably takes place. On the other hand, it cannot take place unless host and invader are in contact at, at least, an approximate balance for periods longer than the ordinary acute infectious disease. During the rapid rise of an epidemic, therefore, while the organisms responsible are passing rapidly through a large series of susceptible individuals in whom death or recovery takes place, the virus transmitted rapidly from person to person,

developing its offensive properties to a high degree, overcomes the defenses of its new hosts too rapidly to permit of much mutual adaptation. Later, as the community becomes more resistant, infections are apt to become more subacute and chronic and carriers may be established, and under such conditions the process of biological adaptation which in the course of time may result in conditions almost symbiotic, are perhaps responsible for the entirely altered manifestations of epidemics.

It is quite possible, therefore, not only in influenza but in other epidemics, that after the initial wave has reached its peak and the organisms attained full virulence, their subsequent spread consisting in a more and more delayed passage from susceptible to susceptible individual, their sojourn in contact with the tissues and secretions of cases and carriers and the slower and less violent progress of the infections in partially immunized individuals may lead to a gradual adaptation, resulting in a new balance between the invasiveness of the causative agent and the resistance of the individual.

It is quite conceivable, then, that if the immunity is a rapidly fading one, as in influenza, organisms of considerable virulence, smouldering in carriers or in mildly reacting partially immunized individuals, may pass through a new period of violent spread as the susceptible percentage is again developed to a larger extent.

In influenza, we are confronted with a particularly difficult problem in that, as we have seen above, we are in possession of no definite knowledge concerning the causative agent. As far as the influenza bacillus, itself, however, is concerned, while we are, of course, entirely in doubt as to its etiological significance, its unquestionable fluctuations in virulence are of considerable interest. Recently, in our own laboratory, J. T. Parker and Frederic Parker, Jr., studied a meningeal strain of influenza which was obtained originally from the meninges of a child which died at the Nursery and Child's hospital in New York. This organism was kept alive on artificial media for some six weeks and then used in a series of experiments on rabbits. Intratracheally injected into rabbits, this bacillus produced fatal disease, the organism appearing in the pleura and usually in the general circulation of the animals. Within 6 rabbit passages with the pleural exudate of previously killed rabbits, the organisms acquired a virulence so high

that less than 0.05 cc. of pleural exudate would kill the rabbits in a short time, sometimes with pneumonia, sometimes passing through the lungs and causing a general septicaemia without noticeable pathological changes in the lungs. On further preservation in rabbit's blood media for about two weeks longer, this organism again lost its virulence to such an extent that lately large amounts injected into rabbits produced no noticeable effect.

It is not supposed that these considerations will throw any considerable light upon the fluctuation of epidemic waves in influenza, but they are inserted merely to indicate the lines of thought and experimentation along which these problems may eventually be elucidated.

Summary

I have sketched the epidemiology of this disease in a fragmentary way only. I have neither the material nor am I sufficiently versed in statistical studies to go more deeply into this phase of the subject. Furthermore, it is too early to attempt to complete analysis of such records, which are being carefully worked over by statisticians at the present time and will be published in due time with greater accuracy than I could bring to bear upon them.

It is quite probable that influenza will continue to be prevalent in outbreaks of varying intensity all over the world for some years to come, and that the disease will remain endemic in a scattered, sporadic manner for many years after that. May we hope that etiological and epidemiological work which is being followed so assiduously all over the world at the present time will furnish us with more competent methods for prevention and delimination before the world is visited by another pandemic.

The writer is indebted to the surgeon general of the United States army and to Col. J. F. Siler for access to his own military reports and to those of others. A number of helpful suggestions and opinions from Dr. W. H. Frost are also acknowledged with grateful appreciation.

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THE SPECIFIC DYNAMIC ACTION OF VARIOUS FOOD FACTORS

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I. INTRODUCTION

The appetite controls the ingestion of food so that an average man may pass through decades without material gain or loss of weight. The sense of appetite must be an extremely delicate regulator to prevent the gain or loss of body fat through the intake of too much or too little energy in the food.

Life depends upon the continued existence of the component cells of an organism, and these cells must be nourished with food if they are to survive. Phenomena of life are phenomena of motion. The motions within the living cells are maintained at the expense of energy derived from the oxidation of fragments of broken down food-stuffs, that is to say, of disintegrated particles of protein, fat and carbohydrate.

The inquiry, therefore, ultimately concerns the utilization of materials present in the fluid bathing the individual cells.

A broad, clear visioned conception of the underlying fundamentals has been presented by Rubner (33) in his volume on the "Nutritional

Physiology of the Yeast Cell." He presents comparative figures establishing the Law of Surface Area and these may advantageously be studied.

	Calories produced per square meter of body surface in 24 hours at 15°C.
Man	1042
Pig	1078
Dog	1039
Rabbit	917
Guinea-pig	1246
New-born mouse	1122

These comparative values of the heat production per square meter of surface are based upon the general assumption that the surface is a factor of the mass following the formula

$$\text{Surface} = \sqrt[3]{\text{Volume}^2}$$

Those investigators, present or future, who would upset the validity of the law that in the resting mammal the heat production is proportional to the surface area, should demonstrate the falsity of the general relations exhibited above if they wish to establish their case.

Rubner has carried the investigation of the metabolism from the gross results obtained in highly developed mammals to the metabolism which may be computed as arising daily from a square meter of cell surface. These results may be thus summarized:

	WEIGHT	CALORIES PER KILOGRAM	CALORIES PER SQUARE METER CELL SURFACE	CELL SURFACE IN SQUARE METERS PER KILOGRAM
Horse	450.0 kgm.	11.1	0.03	
Man	70.0 kgm.	30.0	0.2	150
New-born mouse	1.0 gram	654.0	3.69	
Yeast cell (38°)	0.000,000,000,5 gram	1743.0	3.0*	600

* Rubner gives this figure as 1.25, which is apparently an error in calculation.

The heat production of a unit of mass of yeast is therefore threefold that of a new-born mouse, 58 times that of a man and 157 times that of a horse.

The heat production per square meter of cell surface, however, is quite the same in the yeast cell and in the new-born mouse, but it is

15 times greater in the yeast cell than in man and is a hundred times greater than in the horse.

Rubner has further calculated the quantity of protein and sugar absorbed by a square meter of cell area and also the quantity of cane-sugar necessary to furnish cells presenting a square meter of surface with sufficient energy for the maintenance of life for 14 hours.

These values may be thus tabulated:

	CALORIES PER SQUARE METER CELL SURFACE	CANE-SUGAR EQUIVALENT GRAMS	PROTEIN FOR MAXIMAL GROWTH PER SQUARE METER CELL SURFACE
Horse	0.03	0.007	0.002
Man	0.2	0.05	
New-born mouse	3.69	0.89	0.030
Yeast cell	3.00	8.38*	0.948

* Anaerobic.

The yeast cell achieves its maximum activity in solutions of cane-sugar which vary between 2.5 to 20 per cent in concentration. Within these limits the fermentation process is independent of the concentration of the solution. When the yeast cells are suspended in a solution of cane-sugar having a strength of 20 per cent., the quantity of sugar contained in a film 0.04 mm. thick would afford a sufficiency of nourishment for their support during twenty-four hours. In like manner it may be calculated that in man, whose cells are bathed in a liquid containing 0.1 per cent of sugar, the quantity necessary to support life for the period of one day would be contained in a layer which, if spread around a cell, would have a thickness of 0.05 mm.

If one continues this manner of calculation it may be estimated that the quantity of sugar in a 0.1 per cent solution necessary fully to maintain an average active cell in the human body during a period of one minute would be present in a film 1/300,000 mm. thick or one having approximately 1/200 of the diameter of a red blood corpuscle. It is probable that the entire circuit of the blood is accomplished in between twenty and thirty seconds. The blood plasma in man is separated from the tissues by a capillary wall so thin that no computation of its size has been made. The existing experimental evidence

indicates that there is no oxidative disintegration with resultant heat production in the blood itself. The blood stream is the transportation system to the ultimate consumers, which are the individual tissue cells.

One can therefore picture a tissue cell whose requirement for maintenance for a minute may be held in a film of fluid containing 0.1 per cent sugar solution having the thickness of 1/200 the diameter of a blood cell, and that this fluid may be replenished through an indeterminably thin capillary wall by the diffusion of materials such as sugars, fats and amino-acids passing in a constant stream, no part of the current of which rests in a given capillary for a time exceeding two seconds. One can well imagine that if the nutrient fluid should contain food particles in abundance, the nutritive condition in the cells might be modified thereby. In what way do these body cells react to an increased bombardment by glucose, by fat, by glycocoll, by alanin, by acetic acid or by lactic acid? And how are the results obtained to be interpreted?

In 1913 Rubner (34) spoke as follows in the Prussian Academy of Sciences:

> To follow nutrient particles to the cells, to measure them quantitatively and to vary them experimentally, belongs to the unsolved problems of today. It is scarcely to be expected that the difficulties standing in the way will soon be overcome.

Though the methods employed be crude and the results obtained be often merely suggestive, yet it is these problems with which the present paper deals.

Under conditions of fasting or under "post-absorptive" conditions when there is no longer any food in the intestine, when the sugar content of the blood is regulated by the liver, when amino-acids are produced in but small quantity, when fat is available in probably restricted amount, if, under these conditions, the heat production of the quiet, resting organism be determined, it will be found that a constant level of minimal metabolism has been established. This level is known as the *basal metabolism.* Ingestion of the three classes of the food-stuffs, whether these be fats, carbohydrates or proteins, increases the quantities of fats, of sugar or of amino-acids in the

blood and therefore in the nourishing plasma surrounding the tissue cells and, under these influences, the production of heat by an animal increases, as may be measured by weighing the oxygen absorbed or by determining directly the heat produced. The increase of heat production under these influences is different with the different kinds of food-stuffs administered. Rubner has defined the increase in the heat production of the organism under the influence of a food-stuff as being the *specific dynamic action* of that food-stuff. It is necessary to picture the plethora of the particles of a food-stuff reaching the living cells and to consider the reaction of the cells to this changed nutritive environment. In other words, the heat production increases when there is a heightened concentration of glucose or of fat or of certain amino-acids in the nutrient fluid bathing the cells of the organism. What is the cause?

A. Rubner's conception of the specific dynamic action of food-stuffs

One of the earliest papers by Rubner (35) is entitled "The Substitution Values of the Principal Organic Food-stuffs in the Animal Body." In this paper the constancy of the fasting metabolism is noted and Rubner comes to the conclusion that when fat, carbohydrate or protein is ingested, each replaces in the body metabolism isodynamic equivalents of body fat or body protein which would otherwise have been consumed in fasting. In other words, 100 calories contained in ingested fat would prevent the destruction of 100 calories contained in body fat, or 100 calories contained in sugar would have effected the same result. This was the basis of Rubner's *isodynamic law*. Throughout Rubner's writings one finds this conception of a fundamental *basal metabolism* attuned to the minimal requirements of cell life, upon which other forms of metabolic activity are superimposed.

When at a later date he (36) formulated the doctrine of the specific dynamic action of the individual food-stuffs, Rubner held to the conception that the basal metabolism was not itself augmented by the ingestion of food, but that it was supplemented by the addition of heat resulting from the cleavages and oxidations of minor fragments produced in the destruction of food particles. According to Rubner

when 100 calories are administered to a dog in the form of sucrose (cane-sugar), the heat production is increased by 5.8 calories. He illustrated the formation of this small quantity of extra heat by comparing it with the quantity of heat eliminated when glucose and fructose are formed as cleavage products of sucrose. He believed that similar cleavages of ingested fat produced the extra 12.7 calories which he observed were liberated in the body when 100 calories in fat were ingested. His conception was that the basal metabolism was satisfied by the utilization of sugar or fat radicles, and that any heat produced aside from that was extra heat which did not involve cellular dynamics. His subsequent discovery that during the life of the yeast cell the major part of the energy is liberated within the yeast cell itself and a small part only is due to enzymotic fermentation outside of the cell, contributed to his mental picture of the strictly dual character of (1) the satisfaction of the fundamental energy requirement and (2) the production of extra heat (36a).

When protein was administered to a dog Rubner interpreted the very great increase in the heat production as being due to the fact that only a part of the protein metabolized could be used to furnish the basal metabolism with life giving energy, whereas a goodly portion of the fragments of the amino-acids were oxidized so that they yielded free heat which could not be utilized for cellular dynamics. For example, in so far as sugar was produced from protein it could be used in the service of the maintenance of the basal metabolism.

Rubner (36) furthermore discovered that the great rise in protein metabolism which Lusk had shown to be a feature of the metabolism in phlorhizin glycosuria in a fasting dog was accompanied by a greatly increased heat production although no protein had been ingested. Rubner calculated the increased heat production for every 100 calories of protein ingested or metabolized, as follows:

	Increase in calories
Meat protein	30.9
Gelatin	28.0
Body protein (phlorhizin glycosuria)	31.9

A very important relation brought out by Rubner is that when the environmental temperature is lowered in the fasting dog the heat production is thereby increased, but such an increase does not take

place if the dog has been given meat in quantity. The following experiment illustrates this point:

ENVIRONMENTAL TEMPERATURE	FOOD	CALORIES PER KILOGRAM
7°	None	86.4
30°	None	56.2
7°	81 calories in meat per kilogram of dog	87.9
30°	81 calories in meat per kilgoram of dog	83.0

The basal metabolism in this instance was 56.2 calories. On reducing the environmental temperature from 30° to 7° it was increased through the reflex influence of cold (the *chemical regulation of temperature*) to 86.4 calories. On giving meat the heat production rose from 56.2 to 83.0 calories if the environmental temperature were 30°. But if the meat were given at an environmental temperature of 7° the heat production was 87.9 calories or practically the same as 86.4 calories found when the dog was fasting in the cold. This experiment reinforced Rubner's doctrine of a fundamental basal metabolism which must be provided with definite fuels. The condition of extra heat requirement, such as is produced through the influence of cold, could be supplied not only from the body stores of fat in fasting, but also from those extra heat producing metabolites of protein which are not directly concerned in the support of cell life.

The theory of Rubner appeared fascinating and was wholly accepted by me in the first two editions of the "Science of Nutrition."

An important contribution of Rubner to the subject of the increased heat production after giving food was the demonstration that the factor of intestinal activity, "Darmarbeit" in the sense of Zuntz (27), had nothing whatever to do with the rise in heat production Thus Rubner (36) demonstrated that administration of bones or of Liebig's extract of beef or of the quantity of water contained in the meat previously given to the dog were without influence upon the production of heat.

Lusk (20) has shown that when urea is given there is no increase in the heat production and that sodium chloride is also without influence.

The absence of "Darmarbeit" as a factor in the specific dynamic action of food-stuffs has been confirmed by others. The work of

Benedict (6) showed that cathartics administered to men caused no increase in the basal metabolism. Johansson (17) showed that administration of glucose to a fasting man or to a diabetic individual might cause no increase in the elimination of carbonic acid, because the greater quantity of the glucose in the first instance deposited as glycogen, and in the second instance was eliminated unoxidized in the urine. Lusk (21) has also shown that the administration of glucose (up to 70 grams) or of fructose to a dog rendered diabetic by phlorizin does not increase the heat production of the animal. The extra heat production after giving sugar is therefore due neither to the absorption of the material nor can it be due to extraordinary kidney activity. Since the cells of the body are readily permeable to glucose and since glucose must diffuse into them after its administration in phlorizin glycosuria, it is evident that the phenomenon of osmosis does not contribute an increase in the heat production. This is reinforced by the fact already stated that the administration of a solution of common salt is without effect upon metabolism.

The conclusion is therefore warranted that an increased metabolism is due to the interrelation between the food-stuffs brought by the blood stream and the metabolizing cells themselves.

B. A critique of Rubner's experiments

The third edition of Zuntz and Loewy's "Lehrbuch der Physiologie" (1920) contains an article written by Zuntz on "Stoff und Kraftwechsel" which must have been revised just before he died. In this he writes:

> It follows from the comprehensive experiments of Mangus-Levy (25) that the rise in metabolism after the ingestion of fat is about 2.5 per cent of the calorie content of the same; about 9 per cent after giving starch; about 17 per cent after giving protein.
>
> Rubner found similar values.

However, Rubner's values were quite different.

	per cent
After cane-sugar	5.6
After fat	12.9
After protein	30.0

Rubner's work was based upon metabolism experiments which continued for twenty-four hours and therefore the finer transitions which can be measured from hour to hour were not observed. No record was kept of the bodily movements of the dog within the box, and in the course of twenty-four hours this might, under certain circumstances, have become an important factor. Furthermore, in Rubner's experiments 30, 31 and 32 in which he fed to the dog a given quantity of meat, the metabolism rose 21.8 calories per kilogram of body weight and in experiments 37 and 38 the same quantity of meat ingested caused it to rise only 16.3 calories. These two figures were averaged in the computation of Rubner's results. Another element open to criticism has been set forth on another occasion. Rubner (36) himself showed that when protein is added to the body it exerts no specific dynamic action and this has been beautifully confirmed in my laboratory by Hoobler (16) after he administered "Eiweissmilch" to a baby. Rubner based his calculations of the percentage quantity of extra heat production upon the calories contained in the meat ingested, although it would appear that the controlling factor is in reality dependent wholly upon the quantity of extra protein metabolism over and above that which occurs in fasting.

If I take the values found in my laboratory and calculate them according to Rubner I find the following figures:

100 calories ingested as protein of meat increase heat production 30.0 calories (43)
100 calories ingested as fat increase heat production 4.1 calories (28)
100 calories ingested as glucose increase heat production 4.9 calories (20)

If, however, the intensity of the specific dynamic action be measured by subtracting the calories of protein of the basal metabolism from those of the hours after giving meat, and determining what relation these *extra* calories of protein metabolism bear to the total increase in calories for the hour, one finds the following relations (43):

Food	*Every extra 100 calories of protein metabolized increases the heat production in calories*
1200 grams meat	45
700 grams meat	48

This calculation merely assumes that the portion of ingested protein which is not metabolized but which replaces the "wear and tear"

quota of the basal protein metabolism contributes no part to the "specific dynamic action" of protein. One must conclude, therefore, that about one-half of the calories of the extra metabolized protein contributes to increasing the heat production of the body. Since Lusk has shown that 51 per cent of the calories of meat protein may pass through a glucose stage, this calculation would of itself be a most perfect demonstration of Rubner's contention that the glucose obtained from protein may be used for the support of the basal metabolism, whereas the other fragments burn, liberating pure heat. Rubner's observation that the elevation of the level of metabolism was proportional to the quantity of meat given, is confirmed. The regularity of the appearance of a definite proportion of extra heat certainly gives intellectual foundation to the theory of Rubner that a part of the calories latent in protein always follows a given course.

As regards the interpretation given by Rubner of the extra calories formed by cleavage after the ingestion of fat, the suggestion is less clear, for in fasting the body lives principally upon its own body fat though at a lower level of metabolism than prevails after fat ingestion. Ingested glucose also causes a specific dynamic action, though glucose is always present in the blood and available for the production of cellular energy.

Recent experiments in my laboratory conducted with modern methods have traced the metabolism process in hourly periods and have confirmed and extended many of the early and often neglected experiments of Magnus-Levy published in 1894. It has been our experience that the experimental work of both Rubner and Magnus-Levy is accurate, but in the light of newer facts other interpretations follow.

In the account hereafter given the experimental evidence is based largely upon the author's own experience. The historical background has been presented above and more fully in the "Elements of the Science of Nutrition."

II. THE INFLUENCE OF CARBOHYDRATE ON THE HEAT PRODUCTION

It is nearly forty years since Carl Voit (41) with prophetic insight wrote as follows:

The mass and capacity (Leistungsfähigkeit) of the metabolizing cells, on the one hand, and the quality and quantity of the food materials brought to them, on the other, determines the height of metabolism; however, the cells can only be active within certain given limits beyond which an additional food supply can no longer be destroyed.

The principal changes in metabolism are induced by the differences in the quality and quantity of the materials used by the cells as brought to them in the circulating blood. The quantity of protein brought in the blood stream is the especially influential factor, but the non-nitrogenous substances are also concerned.

These words of Voit were penned before it was conceived that the protein molecule is a mass of amino-acids bound together. Furthermore, he wrote

The requirement for energy cannot possibly be the cause of metabolism any more than the requirement for gold will put it into one's pocket. However, the production of energy has a very definite upper limit which is afforded by the ability of the cells to metabolize (42).

When glucose is given to a dog it is rapidly absorbed. Fisher and Wishart (13) found that after the administration of 50 grams of the substance in 150 cc. of water the material was nearly all absorbed within the first three hours and completely so during the fourth hour. During this last hour two things happen—a large volume of urine (100 cc.) is eliminated and glycogen in increased quantity is deposited in the liver. During the second, third and fourth hours the metabolism rises about 20 per cent but falls to the basal level during the fifth hour. It is found that the level of blood sugar rises during the first hour but, though it returns to normal thereafter, there is a dilution of the blood, as indicated by a reduced percentage of hemoglobin. The greater volume of more dilute blood therefore carries a greater largesse of blood sugar to the cells than before. The respiratory quotient during the third, fourth and fifth hours is unity, indicating that the source of energy for the living cells is glucose. With the cessation of absorption the liver assumes control of the distribution of sugar molecules in the blood stream, the respiratory quotient falls, indicating a resumption of the oxidation of fat as well as sugar by the cells and the metabolism returns to the basal level.

These factors have led me to define this form of metabolism as the *metabolism of plethora*. Voit stated that an increase in metabolism was dependent on the flow of metabolizable material to the cells. And he also stated that the intensity of the metabolism has a well defined upper limit beyond which it was uninfluenced by additional excess of nourishing materials. This has been substantiated in the following experiments (20).

	GLUCOSE INGESTED	RISE IN METABOLISM IN SECOND HOUR	R. Q.
	grams	*per cent*	
Dog XVIII	8	0	0.91
Dog II	20	15	1.08
	50	20	0.98
	75	20	1.05
Dog I	103	20	1.02

When 8 grams of glucose were given the material caused only a slight increase in the respiratory quotient and there was evidently no such overwhelming of the body cells with an excess of sugar molecules as to cause their utilization to the exclusion of fat. In the other cases, however, the sugar was given in sufficient quantity to cause respiratory quotients near to unity or over, which demonstrates the exclusive combustion of carbohydrate instead of fat. When 50, 75 or 100 grams of glucose were given the same height of metabolism was always attained. This confirms Voit and also is in line with Rubner's discovery (see p. 313) that within wide limits the intensity of the metabolism of yeast cells is independent of the concentration of the sugar solution in which they are living.

It should be remembered that all sugars diffuse with great rapidity throughout the body. Thus, if lactose, which can not be oxidized in the body, be introduced intravenously into a dog, it is found that within half an hour 75 per cent of the injected material has diffused into the tissues (40). But it is not this movement of sugar molecules but their oxidation which is the cause of the specific dynamic action of carbohydrate, for it has been shown (21) that when 70 grams of glucose are given to a dog rendered diabetic with phlorhizin, the

respiratory quotient may remain at 0.72 instead of rising to 1.00, the urinary sugar may rise from 1.5 to 7.9 grams per hour, and yet with all this movement of sugar molecules within the diabetic organism the heat production of the dog remains unchanged.

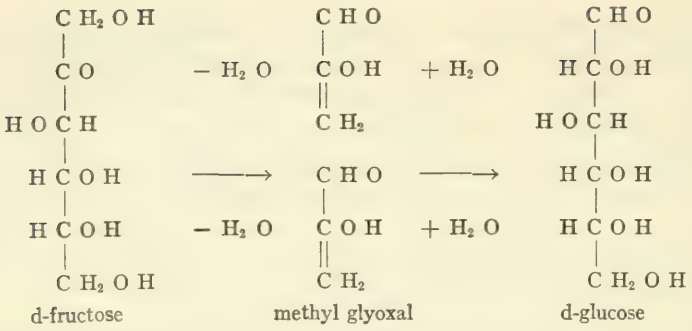
Johansson (17) has shown that when glucose is given to a man after prolonged fasting the carbonic acid elimination is not increased through a deposition of glycogen in the body. This experiment demonstrates that when glycogen is deposited in the organism there is no appreciable increase in the heat production.

In another series of experiments the differentiation in the behavior of various carbohydrates has been investigated. The results obtained are set forth in the following table:

The relative influence of 50 grams of glucose, fructose, sucrose, galactose and lactose upon metabolism

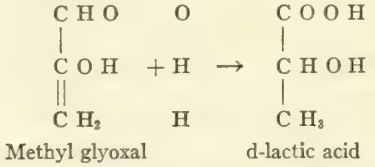
SUGAR	AVERAGE R. Q.	HOURS 2, 3 AND 4 INCREASE OVER BASAL PER CENT
Glucose, 50 grams	1.00	30
Glucose, 70 grams	1.04	35
Fructose, 50 grams	1.02	37
Sucrose, 50 grams	1.02	34
Galactose 50 grams	0.93	22
Lactose 50 grams	0.90	3

In this dog it is apparent that milk sugar was not utilized, probably because of the absence of lactase from the dog's intestine. It was also noted that galactose caused a lesser rise in metabolism than did either glucose or fructose, and the respiratory quotient shows this sugar to be less readily oxidized than are glucose and fructose. Of the latter two, fructose has a slightly greater power to increase metabolism than is possessed by the same amount of glucose. This attribute of fructose may lie in the fact that it must be transformed into smaller molecules before it can be converted into glucose and laid down as glycogen, whereas ingested glucose may be directly removed from the body fluids and be converted into glycogen. The formula for the conversion of fructose into glucose may thus be written:



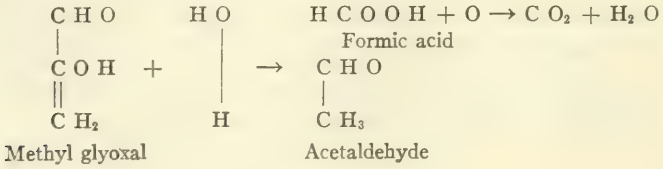
That methyl glyoxal is an important intermediary product of carbohydrate metabolism has been especially emphasized by Dakin (10) who finds that tissue rapidly converts it into lactic acid in vitro, and that it is converted into glucose and eliminated in the urine when given to a phlorhizinized dog.

If one looks further into the subject of the intermediary metabolism of carbohydrate it appears that, although methyl glyoxal may be readily converted into lactic acid according to the following formula,

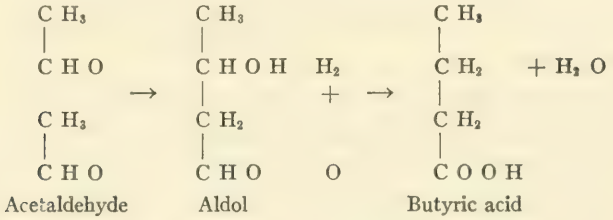


yet, Levene (19) has shown that neither tissue nor leucocytes will oxidize lactic acid further.

It was originally suggested to Magnus-Levy (26) by Spiro that acetaldehyde might be an intermediary product of lactic acid metabolism. If methyl glyoxal underwent this transformation the formula would read as follows:



Spiro propounded this pathway of sugar destruction as a possible explanation of the synthetic construction of fat from carbohydrate, which, written in its simplest form, would present the following chemical changes:



Stepp (40a) finds that after the ingestion of a large quantity of carbohydrate the results obtained on analysis of blood serum for sugar by the optical and the reduction method do not agree and offers this as evidence that acetaldehyde radicles are present in the blood under these circumstances.

It is interesting to note at this point that, whereas acetaldehyde is convertible into glucose in the phlorhizinized dog,[1] as shown by Ringer (31), yet if it be oxidized to acetic acid (32) or reduced to ethyl alcohol (15) or by hydrolysis be converted into butyric acid (30), it is then no longer convertible into glucose.

Ringer (31) believes that acetaldehyde is the main antiketogenic substance derived from carbohydrate metabolism, and that it reacts with β-hydroxybutyric acid to form a substance containing six carbon atoms three of which are convertible into glucose.

It has been shown that when alcohol (21) or acetic acid (unpublished, see p. 335) are given with glucose to a dog the heat production rises above the level manifested when glucose alone is given by the addition of that increment of heat which either ethyl alcohol or acetic acid, when given alone, would have induced. Therefore, it seems that these two substances must be affinities of their own in the heat augmentation process which are not affected by the cleavage products of glucose. If one conceives a cleavage of carbohydrate with the production of acetaldehyde molecule, one must consider it probable

[1] My colleague, Stanley R. Benedict, has found the conversion of acetaldehyde, to be complete in the phlorhizinized dog (Unpublished; quoted by permission).

that there is a limit beyond which its oxidation through acetic acid is not effected.

Still other unpublished experiments show that, although lactic acid ingested alone may increase the heat production, yet when given with glucose there is no augmentation above that which glucose alone produces. This is because its metabolites are of the same order as those of glucose.

The picture that presents itself, therefore, is that a glucose molecule carried by the blood stream rapidly diffuses into the cells, that it may be broken in two within the cells into methyl glyoxal molecules, thereby increasing the number of metabolizable compounds and also their chemical lability. The next step might be the conversion of methyl glyoxal into formic acid, which might at once be oxidized, and into acetaldehyde, which when present in excess of the requirement of energy for the cell might react with formic acid and be condensed into fat. Its oxidative pathway through transformation into acetic acid would then be inhibited.

Remembering these possibilities, one can consider the bearing of certain experimental results upon the interpretation of the cause of the specific dynamic action of carbohydrates. For one may explain the slightly greater increase in the metabolism of the dog after giving fructose than after giving glucose by imagining that the whole mass of the ingested fructose becomes available for the maintenance of cell activity because it must, perforce, pass through the methylglyoxal stage, whereas glucose itself could have been laid down directly as liver glycogen and thereby could have reached the blood stream and the tissue cells in lesser concentration than fructose would have done.

If carbohydrate be given in considerable quantity at a time when the glycogen reservoirs are filled and the body cells have reached their *optimum* of carbohydrate destruction, then carbohydrate is converted into fat. Such fat production may be illustrated by the following formulae:

$$\underset{\text{Glucose}}{C_6H_{12}O_6} + O_2 = \underset{\text{Butyric acid}}{CH_3(CH_2)_2\,COOH} + 2CO_2 + 2H_2O$$

$$\underset{\text{Glucose}}{4C_6H_{12}O_6} + O_2 = \underset{\text{Palmitic acid}}{CH_3(CH_2)_{14}\,COOH} + 8CO_2 + 8H_2O$$

The respiratory quotient when palmitic acid is formed from glucose would be 8.0. Bleibtreu (7) took into consideration the production of the glycerin and fatty acid content of animal fat and wrote the formula:

$$\begin{array}{l} 270.6 \text{ grams glucose} = 100 \text{ grams fat} + 115.45 \text{ grams } CO_2 + 54.6 \text{ grams } H_2O \\ 997.2 \text{ calories} \quad\quad = 950 \text{ calories} \end{array}$$

I have added the caloric values and have estimated that 4.7 per cent of the original heat content of the glucose was lost in its chemical transformation into fat. From this it may be estimated that for every liter of carbon dioxide eliminated 0.80 calories are produced. Similar calculations were made by Magnus-Levy (25) in 1894, who used a formula written by Hanriot (14). He concluded that there was very little extra heat production when either carbohydrate or protein was converted into fat. That this was a true conclusion was proved by Lusk (21) from experiments in which he gave 70 grams of glucose to a dog. In one of the experiments (no. 91) the results may thus be calculated:

	HOURS AFTER GLUCOSE			
	2	3	4	All 3
Indirect calorimetry	24.52	24.91	24.81	74.41
Indirect calorimetry (corrected)	24.78	25.38	25.49	75.65
Direct calorimetry	25.31	25.63	25.12	76.06
Respiratory quotient (non-protein)	1.08	1.14	1.16	

It is evident that the correction of the heat production on account of the transformation of carbohydrate into fat introduces only a slight element of increase in the sum total of heat produced. That the calculation is sound is confirmed by the agreement between the calculations thus made and the heat as determined by direct calorimetry.

In the above experiment 1.73 liters of extra CO_2 were expired by the dog as the result of converting 8.1 grams of glucose into 3 grams of fat. In another experiment (no. 90) the production of fat from sugar was only half the above quantity, though the metabolism was practically at the same level, 75.30 calories in three hours.

It is therefore evident that if the level of optimum metabolism is reached, the process of conversion of carbohydrate into fat involves the cells of the organism in virtually no additional heat production.

It has been suggested that acid radicles are the cause of the increase in heat production; that they stimulate the cells after carbohydrate ingestion. However, it was first shown in my laboratory by A. L. Meyer that the CO_2 combining power of the blood plasma was unchanged after giving glucose in large quantity, and repeated experiments have recently confirmed this observation. Moreover, it has also been discovered that after giving hydrochloric acid sufficient to reduce the CO_2 combining power of the blood plasma from 54 to 48 volumes per cent of CO_2 in the blood plasma, the metabolism is only very slightly increased and not at all to such an extent as is effected by glucose ingestion. It has also been suggested that when fructose is given to a diabetic the heat production is increased through the stimulating effect of acid intermediate products (5). However, Lusk (21) found no increase in the heat production of a phlorhizinized dog after giving 10 grams of fructose which was largely converted into glucose and eliminated in the urine. The intermediary metabolite, probably methylglyoxal, exerts, therefore, no stimulating effect upon the heat production. This result has been confirmed by Falta (12) in experiments on man.

Another experiment (2) of especial significance is, that when 70 grams of glucose are given to a dog and the dog forced to run at a rate of 4800 meters per hour (3 miles), the heat production of the animal is slightly less than when the animal runs in the morning without food (see p. 336). Even on the thirteenth day of fasting the cost of energy in the dog for the movement of 1 kgm. of his body weight one meter is the same as when the animal is well nourished. This may be expressed thus:

	WORK IN KILOGRAMS TO MOVE 1 KGM. 1 M.	R. Q.
Running morning without food	0.578	0.79
Running after 70 grams glucose	0.555	0.92
Running 13th day of fasting	0.584	0.73

The respiratory quotient did not reach unity when the dog ran after glucose ingestion. It is probable that glucose reaching the cells was immediately utilized for the work of the movement and that there was no surplus of metabolizable particles to raise the metabolism of the cells. Certainly, no intermediate metabolites of glucose exercised a specific dynamic effect to lift the cellular metabolism to a higher level upon which the metabolism necessary for muscular effort had to be superimposed.

A. Summary

1. When 50 grams of glucose are given to a dog it is rapidly absorbed and glucose molecules are furnished to the body cells in increased number.

2. All sugars diffuse into the body cells with great rapidity.

3. Increased movement of unoxidized glucose molecules in diabetes is without influence upon the heat production.

4. The deposition of glycogen does not increase the heat poduction.

5. If 50, 75 or 100 grams of glucose be given to a dog it is possible to increase the heat production by 20 per cent above the basal metabolism during the hours of glucose absorption, but increasing the quantity of glucose ingested does not increase the level of metabolism, which may therefore be described as the optimum level of glucose metabolism.

6. Another dog, whose metabolism had been raised 30 per cent above the basal level after giving 50 grams of glucose, suffered an increase of 35 per cent after receiving 70 grams of glucose and one of 37 per cent after taking 50 grams of fructose. It is suggested that, whereas part of the 50 grams of glucose could have been laid down as glycogen and removed from the circulation, all of the fructose must first break up into methyl glyoxal radicles, thereby increasing the mass of these readily oxidizable metabolites.

7. If carbohydrate be given in excess it may be converted into fat, but this process transpires with only a slight energy loss and does not appreciably increase the total cellular heat production which the already reached its maximum.

8. When lactic acid is given with glucose the total metabolism is not appreciably affected, for lactic acid is directly derivable from glucose and may satisfy the cellular affinities for this material.

9. When acetic acid or ethyl alcohol is given with glucose there is a summation of effect, the metabolism being raised by the sum of the increases which each substance given alone would induce. Possibly acetic acid and alcohol are not metabolites of glucose. If acetaldehyde be a normal product of glucose metabolism, one must conclude that there is a limit beyond which its oxidation through acetic acid is not effected.

10. Ingestion of glucose in large quantity does not reduce the CO_2 combining power of the blood and hence one can infer that acid metabolites are not causative of the increased heat production.

11. When carbohydrate is converted into fat there is a largely increased elimination of CO_2 without concomitant increase in the metabolism. Therefore an increase in CO_2 production can not be a stimulus to increased heat production.

12. The transmutation of fructose into glucose, presumably through methyl glyoxal, does not increase the metabolism in the dog made diabetic with phlorhizin. The mere presence of unoxidixed intermediary fragments of fructose is therefore without influence upon metabolism.

13. Though there is a reduction of the CO_2 combining power of the blood plasma after the ingestion of hydrochloric acid, it has a very slight effect upon metabolism in comparison with that induced by the administration of glucose.

14. When a dog is caused to run at a rate of 4800 meters or 3 miles per hour, the additional energy production for the unit of work is slightly more without food than when 70 grams of glucose are given. The influx of glucose molecules is immediately used in the production of work. There is no excess of metabolites with which to raise the metabolism to a higher level and the intermediary metabolites of glucose, though formed in largely increased measure, exert no specific power to raise the level of that basic metabolism upon which the definite quota of energy necessary to accomplish work is superimposed.

B. Conclusion

One can not escape the conclusion that in the presence of an abundant quantity of oxidizable fragments of carbohydrate metabolism the heat production is raised to a higher level. Definite affinities for carbohydrate consumption are satisfied which are not involved when the extra supply of glucose is being continually depleted under the influence of work or is reduced, as in fasting, when the blood stream is under the regulatory control of the liver. The production of increased heat after carbohydrate ingestion may be termed the *metabolism of carbohydrate plethora.*

III. THE INFLUENCE OF FAT INGESTION UPON THE HEAT PRODUCTION

In the experiments of Magnus-Levy already cited glucose was given to a dog at the same time as lard and therefore the results obtained are not technically above reproach.

Murlin and Lusk (28) made a study of the behavior of the metabolism of a dog after administering an emulsion of fat and noted also the influence upon the metabolism when fat and glucose were administered together. The results obtained are shown in charts I and II.

It appears that when fat alone is administered the heat production gradually rises until about the sixth hour when it reaches its maximum and then gradually falls until the twelfth hour when the basal level is regained. The maximum level of metabolism is 30 per cent above the basal level. The work of Bloor (8) has shown that after giving fat to a dog there is a gradual rise in the fat content of the blood, the maximum being attained in the sixth hour, after which there is a fall. Here, then, as in the case of glucose ingestion the metabolism is influenced by the mass of metabolites reaching the cells.

The respiratory quotients after giving fat were always lower than the general average of such quotients found in the determinations of the basal metabolism with which they were compared. It was calculated that all the extra heat produced was at the expense of an added increment of oxidized fat.

When the fat emulsion containing 75 grams of fat was given together with a solution of 70 grams of glucose there was a primary increase in the metabolism due to the combustion of glucose, as indicated

by high respiratory quotients, and this state was followed by a continuance of the high level of metabolism with a fall in the respiratory

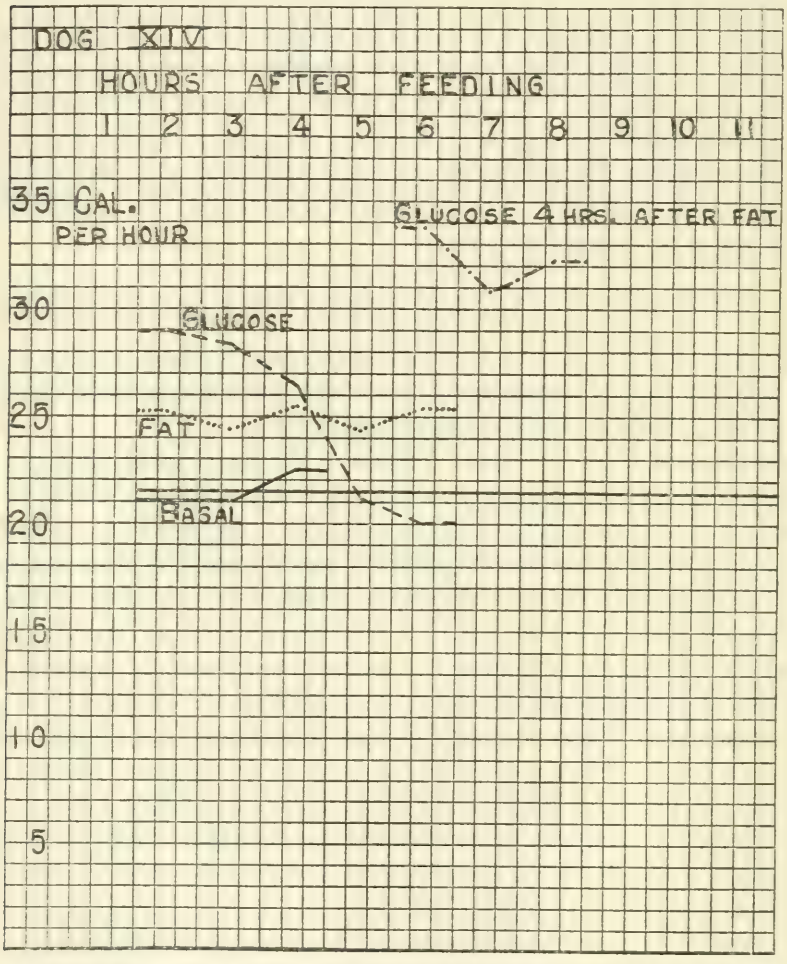


CHART I. THE EFFECT OF FAT, OF GLUCOSE, AND OF GLUCOSE PLUS FAT UPON THE HEAT PRODUCTION (28)

quotients due to the subsequent absorption and combustion of fat. This is the reason why a mixed diet of fat and carbohydrate is satisfying for a longer period than when carbohydrate alone is taken.

The glucose is given four hours after the ingestion of fat, so that the maximum effect of glucose falls at the same time as the maximum

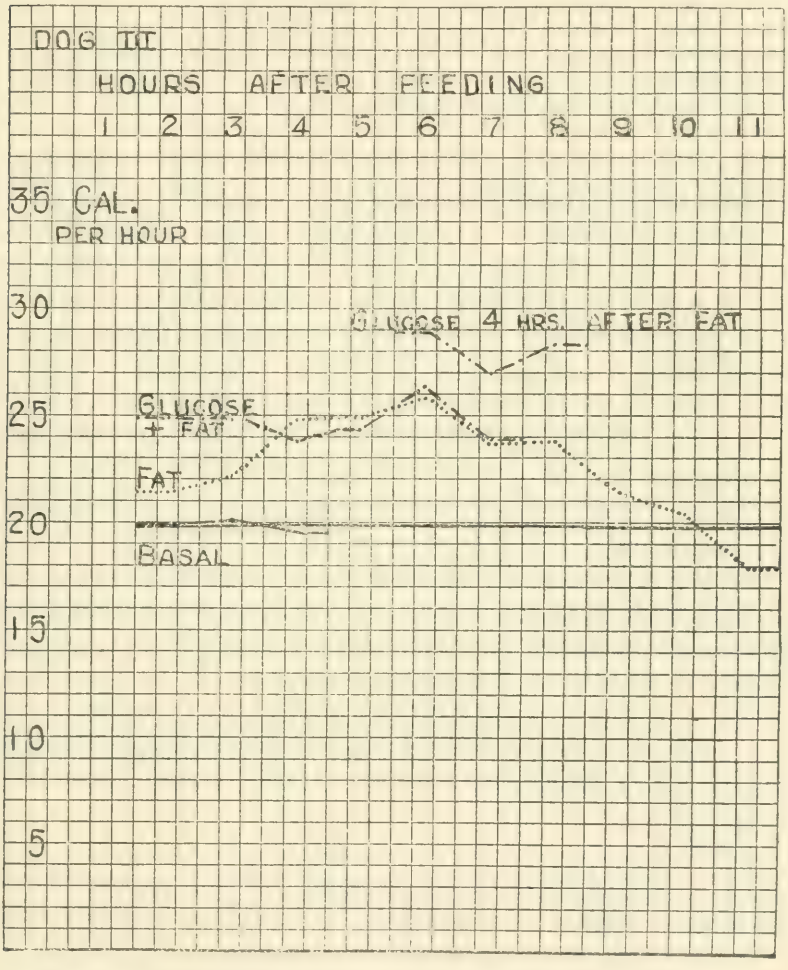


CHART II. THE EFFECT OF FAT AND OF GLUCOSE PLUS FAT UPON THE HEAT PRODUCTION (28)

effect of fat, the resulting increase in the heat production is equal to the sum of the increases which each substance given alone would have induced. This appears as follows:

	R. Q.	CALORIES PER HOUR	INCREASE ABOVE NORMAL	
			Calories	Per cent
Basal	0.85	21.5		
Fat, 75 grams	0.80	25.0	3.5	16
Glucose, 70 grams	1.00	28.6	7.1	33
Glucose 70 grams, four hours after fat, 75 grams	0.93	32.3	10.8	50

It is evident that when carbohydrate is given at the height of fat ingestion, the respiratory quotient is lower than unity and betokens the coincident oxidation of fat and carbohydrate Therefore when these two materials are transmitted through the blood stream together there is a direct summation of effect. Since the metabolism of glucose is at a maximum when 70 grams are given, it follows that for the utilization of fat an entirely different mechanism is invoked. There must be definite individual affinities within the cell which utilize fat metabolites when transported to them in the blood stream.

A question of some difficulty arises at this point. Why should not the fat formed synthetically after glucose ingestion be immediately oxidized as is ingested fat when given with glucose? One can explain this only on the assumption that the synthesis of fat from carbohydrate is limited to a restricted area or locality of body tissue, whereas the oxidation of carbohydrate and of fat is a property common to all tissue. The localized production of fat from carbohydrate is indicated by the fact that, whereas the theoretical respiratory quotient for this reaction is 8.0, the actual quotient obtained from an entire animal after stuffing it with carbohydrate rarely exceeds 1.30.

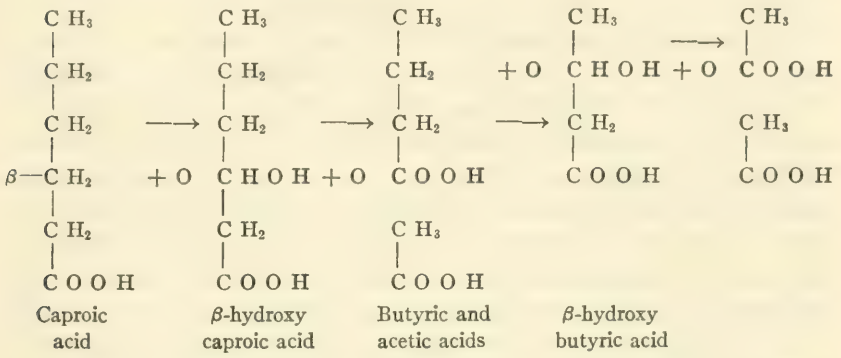
According to the well-known experiments of Knoop (18), fatty acids are oxidized on the β-carbon atom, yielding successively two carbon atom chains. The oxidation of caproic acid would follow the course shown by formula on following page.

If palmitic acid broke up by successive oxidation into acetic acid the following equation would represent its transformation:

$$\underset{\text{Palmitic acid}}{C_{16}H_{32}O_2} + 14\,O = \underset{\text{Acetic acid}}{8C_2H_4O_2}$$

1 gram = 1.348 grams
9.353 calories = 4.706 calories

This reaction involves a loss of heat of 50 per cent. There is nothing to indicate that the energy evolved in the oxidative transformation of palmitic acid is physiologically distinct from that produced in the oxidation of acetic acid itself. The whole of the oxidation process may be affected through the mechanism of a single affinity of the cell.



Recently performed and still unpublished experiments done in my laboratory show that when acetic acid is given with glucose there is an increase in metabolism equal to that produced by the individual substances acting severally. This supports the theory of its being an intermediary metabolite of fat. Acetic acid is quickly absorbed and must be immediately oxidized after absorption, for it exerts no influence upon the CO_2 combining power of the blood.

The results may be thus expressed:

	INCREASE ABOVE BASAL METABOLISM	
	Calories	Per cent
Glucose, 58 grams	+4.71	+27
Acetic acid, 3 grams	+3.13	+18
Sum of both	+7.84	+45
Glucose, 50 grams + acetic acid, 3 grams	+7.23	+41

Diabetic acidosis has its origin from β-hydroxybutyric acid when it is retained in the body as an unoxidized residuum of fat metabolism.

If the condition of acidosis were determinative of a higher level of metabolism after fat ingestion, one would expect that the height of metabolism in diabetes would be proportional to the height of the acidosis. However, in an analysis of 23 cases of diabetes, Allen and Du Bois (1) found that no relation existed between the intensity of acidosis and the height of the metabolism. The patient who had the highest metabolism showed very slight acidosis.

It has already been stated that the energy required to move a running dog was the same per horizontal kilogram meter, whether the energy were obtained from ingested glucose or from the dog's own body fat after the dog had fasted thirteen days. Furthermore, the basal metabolism of this dog was the same on the fifteenth day of fasting when the respiratory quotient was 0.73 as it was after two days of a carbohydrate-containing diet, at which later date the respiratory quotient was found to be 0.93. As sources of energy for the basic needs of the body fat and carbohydrate are therefore mutually interchangeable according to the law of isodynamic equivalents. It is only when the concentration of either or both rises high in the nutrient fluid that the special separate affinities come into play and cause or enable the metabolism to reach higher levels.

The influence of fat ingestion upon the metabolism has been more rigorously investigated than the influence of carbohydrate and of protein have been.

A. Summary

1. The heat production in the dog after giving fat gradually rises to a maximum in the sixth hour, when the increase above the basal level may amount to 30 per cent. It then gradually falls and reaches the basal level in twelve hours after its administration. The sixth hour is the time of the maximum fat content of the blood (Bloor).

2. The additional heat produced is at the expense of the oxidation of fat.

3. When glucose and fat are given together the former is first oxidized, the heat production rises and the respiratory quotient approximates unity; the level of increased heat production continues through subsequent hours on account of the absorption of fat, the respiratory quotient falling on account of the increased oxidation of the latter substance.

4. When glucose is given four hours after the ingestion of fat so that the maximum effect of glucose ingestion falls at the time of the maximum metabolism induced by fat, there is a summation of effect, the heat production reaching a level above that of the basal metabolism by the sum of the two several increments which each substance would have produced. The respiratory quotient indicates the metabolism of fat as well as carbohydrate.

5. If glucose and acetic acid are administered together the same summation of effect occurs.

6. Hence, in the presence of an amplitude of fat and of glucose molecules, the affinities entering into the mechanism of the increased destruction of either appear to be separate and different.

7. The reason why fat, which is synthetically produced from carbohydrate, is not oxidized as is fat when ingested with carbohydrate, may possibly be that the production of fat from carbohydrate may be limited to a restricted area or locality of tissue, whereas the oxidation of carbohydrate or of fat is a property of all tissues.

8. The basal metabolism is independent of the height of the respiratory quotient, and therefore the basic requirement may be supported by isodynamic equivalents of fat or carbohydrate.

9. The severity of diabetic acidosis is no criterion of the height of the metabolism in diabetes.

B. Conclusion

The same conclusion is reached regarding fat as regarding carbohydrate, that in the presence of an amplitude of fat particles there is a *metabolism of fat plethora*, due to the utilization of fat by special fat receptive cellular affinities.

IV. THE INFLUENCE OF PROTEIN UPON THE HEAT PRODUCTION

The general conclusions reached by Rubner as regards the influence of protein ingestion upon the heat production have been set forth in the introduction. It should be recalled that when Rubner wrote his book, "Die Energiesetze," in 1902 it was still permissible to consider the protein molecule as a complex containing a glucose radicle. It was not until later that the conception of protein as consisting of

a chain of amino-acids came to be generally accepted. At the present time one must not only consider the effect upon metabolism of the ingestion of meat, but also the behavior of the individual metabolites into which the protein may be resolved. The story might be spun into a tale of considerable length, but it may be well here to emphasize only the more significant points.

After giving 1200 grams of meat to a dog weighing 13.5 kgm. Williams, Riche and Lusk (43) determined the hourly heat production by both direct and indirect calorimetry. The results are presented in the accompanying diagram (chart III). The basal metabolism measured 22.3 calories but after giving meat it rose to a height of 36 calories in the second hour and to 42 calories in the third hour, a maximum increase above the basal of 88 per cent. The heat production was maintained at a level above 40 calories through the tenth hour. In the fourteenth hour it had fallen to 37 calories and then remained at 30 calories up to the eighteenth hour, falling rapidly to 25 calories in the twenty-first hour.

Except in the earlier hours of the experiment the curve of urinary nitrogen elimination is quite parallel to the heat production. The small elimination of urinary nitrogen in the early hours is due to the accumulation of urea within the blood and tissues and not to a much lower protein metabolism.

During ten hours of the experiment the quantity of carbon eliminated in the respiration was less than the amount which would have been so eliminated had the protein metabolized, as measured by the nitrogen in the urine, been wholly oxidized. This carbon retention amounted to the equivalent of a retention of 34.5 grams of glucose. Calculated on the presumption of this retention of glycogen from the protein metabolism of the period, the oxygen absorption should have been 184.55 grams. Actually consumed, there were 186.2 grams of oxygen. If carbon had been retained as fat only 169.7 grams of oxygen would have been required. It is therefore apparent that glucose may be formed normally from protein and not merely in diabetes as a pathological by-product.

As a second illustration of this phenomenon, McCann (24) has shown that the administration of the protein of meat to a normal man on the eleventh day of fasting resulted in the initial establishment

of respiratory quotients of 0.68 in two successive hourly periods. The quotients betoken the retention as glycogen of the whole of the glucose formed from protein, for they are quotients hitherto obtained

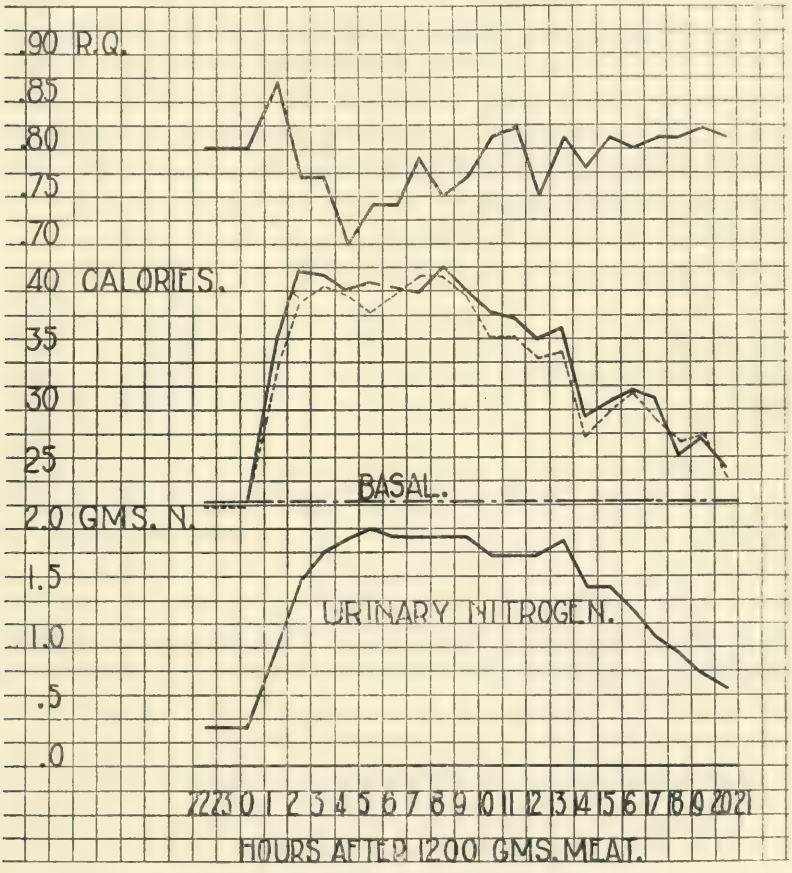


CHART III. SHOWING THE RESPIRATORY QUOTIENT

The total metabolism by indirect calorimetry (solid line), by direct calorimetry (dotted line) and the nitrogen elimination during hourly periods after the ingestion of 1200 grams of meat by a dog (43).

only in severe diabetes under circumstances in which the sugar derived from protein was not oxidized but was eliminated in the urine. The greedy cells of the fasting body laid hold of the sugar produced from protein and deposited it as glycogen.

It has already been shown that the deposition of glycogen is effected without increasing the heat production.

Conditions, however, may be such that fat also may arise from protein. Thus, in certain experiments (23a) the basal metabolism of a dog was determined and then 1000 grams of meat were given in the early morning, the standard diet containing 75 grams of carbohydrate in the evening, and again 1000 grams of meat the following morning. These conditions would tend to produce glycogen saturation of the repositories for glycogen in the body and the carbon retained from protein might then be laid down in the form of fat, as is set forth in the following analysis:

	INDIRECT	DIRECT
Basal metabolism per hour	14.25	14.31
1000 grams meat, average fifth, sixth, seventh hours	27.55	28.44
Increase	93 per cent	

The respiratory quotients of the retained pabulum were calculated to be 0.708, 0.688, 0.685, betokening a deposit of fat. Had the 0.84 gram carbon, which was retained hourly, been deposited in the form of glucose, indirect calculation would have shown 30.30 calories to be the heat production. The evidence is therefore that protein carbon can be synthesized both into glucose or into fat and retained in the body as such. It has been shown that the production of fat from glucose takes place with the formation of but little extra heat liberation and here the same process must prevail.

Following the ingestion of 1000 grams of meat given to the animal mentioned above, the respiration rate rose from a basal level of $7\frac{1}{2}$ per minute to $23\frac{1}{2}$ per minute, the animal resting quietly throughout.

A great increase in the heat production may also be observed in man after taking meat in large quantity, though the rise is not as great as in the dog. A dog weighing 10 kgm. may devour 1000 grams of chopped meat within a minute, whereas it requires about half an hour or more for a man to take 660 grams of the same material. In the dog the protein metabolized may be of greater energy value than the total heat production, whereas in man only a fraction of the total heat production will be derived from the meat ingested. The follow-

ing chart (chart IV), showing the influence of the ingestion of 660 grams of meat by (1) a normal man, (2) an achondroplastic dwarf, and (3) a legless man, is taken from the work of Aub and Du Bois (4).

It appears that the sulphur elimination precedes that of nitrogen, illustrating the presence of a lag in nitrogen elimination. In the achondroplastic dwarf there is a maximal increase in the heat production of 46 per cent above the basal level. This increase is not relatively as large as in the dog, but the difference observed is probably due to the limitations of the digestive tract. The dog mentioned in the last experiment would never partake of more than 1200 grams of meat at one time, and the upper limit of metabolism must have been nearly or quite reached in the case described.

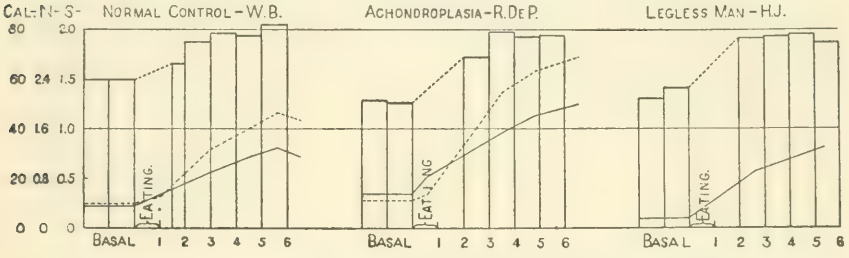


CHART IV. ILLUSTRATING THE SPECIFIC DYNAMIC ACTION OF PROTEIN IN MAN

The columns show the basal heat production in calories per hour rising after the subject has eaten meat containing 23 to 25 grams of nitrogen. The dotted line represents the excretion of sulphur in the urine in decigrams, the continued line, the nitrogen elimination in grams per hour (4).

Whereas, as in the dog, it was noted that after giving meat the increase in heat production might amount to 50 per cent of the calories of the extra protein metabolized, in man it was discovered that fully 75 per cent of the energy content of the extra protein metabolized reappeared in the form of the heat of specific dynamic action. It is obvious that a meat diet is physiologically wasteful.

In the achondroplastic dwarf, with large body and short legs, and in the legless man the specific dynamic effect of protein was more in evidence than in the normal controls. Possibly this may have been due to the fact that in the former individuals the liver or some other organ or organs bore a greater proportion to the total weight than normally, and this suggests the possibility that the seat of the

"specific dynamic action" of protein may reside in the liver or some other organ or organs in greater degree than in the muscles.

However, Aub and Means (4a) find that the response of the human organism to the specific dynamic action of meat is just as great in severe cirrhosis of the liver as in the normal condition. They conclude that the liver is not the main site of the specific dynamic action or that it can adequately perform that function even in disease.

The increase in the heat production after protein ingestion greatly transcends that which follows the giving of carbohydrate and fat, and it is of a different character.

One sharply characteristic quality of the specific dynamic action of protein is that when once the level of heat production is increased after giving meat any energy necessary for the production of work is superimposed upon this higher level of metabolism. This was first demonstrated by Rubner (37) in man and may be recorded as follows:

	CALORIES	
	Per day	Increase due to work
No food, rest	1976	
Cane-sugar, 600 grams, + H_2O, 3000 grams, rest	2023	
Same + work (100,000 kgm)	2868	845
Protein, large amount of meat	2515	
Same + work (100,000 kgm)	3770	855

This work was confirmed and extended by Anderson and Lusk (2) and showed that the energy of metabolism was the same when a dog ran 3 miles an hour whether or not glucose had been given in large quantity; also that the energy expenditure required for running was superimposed upon the higher metabolism induced by meat ingestion or by such a fragment of protein metabolism as alanin. This distinction has important theoretical bearing.

Their results may be epitomized as tabulated on following page.

The attractive theory of Rubner is that when protein is metabolized it can be utilized for cell life only in so far as it is convertible into glucose, and that such fragments as are not so converted are oxidized with the production of free heat which is of as little value for the maintenance of the living mechanism as heat produced in the

body through high powered electric currents, for example. The latter form of heat does not alter the fundamental metabolism.

This theory lent itself to experimental proof for Ringer and Lusk (32) found that, whereas glycocoll and alanin were completely converted into glucose in the organism of the diabetic dog, only three of the five and four carbon atoms contained respectively in glutamic and aspartic acids were convertible into glucose.

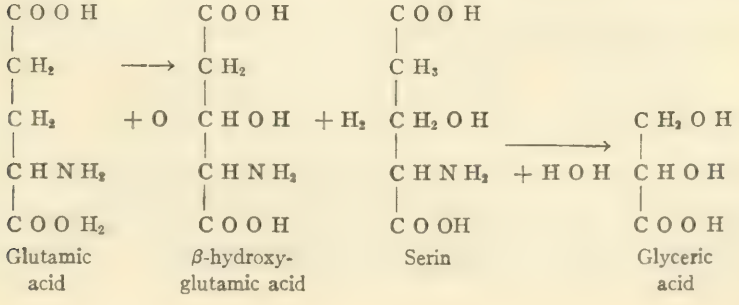
	CALORIES PER HOUR	R. Q.	DISTANCE IN METERS	WORK IN KILOGRAMS TO MOVE 1 KGM. 1 METER
No food, rest	17.2	0.86		
No food, work	76.1	0.79	4806	0.578
Glucose, 70 grams, rest	21.0	1.07		
Glucose, 70 grams, work	77.1	0.92	4771	0.555
Meat, 750 grams, rest	70.0	0.80		
Meat, 750 grams, work	92.4	0.80	4704	0.587*
Alanin, 20 grams, rest	21.0	0.84		
Alanin, 20 grams, work	82.0	0.78	4777	0.583†

* Corrected for influence of meat.

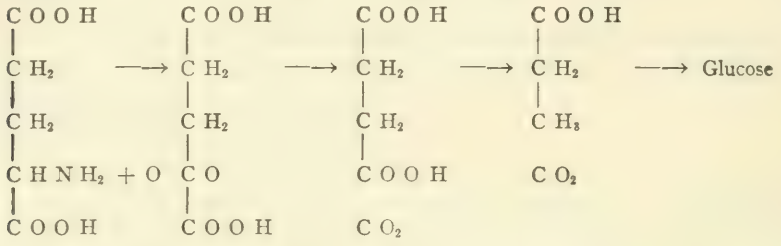
† Corrected for influence of alanin.

Ringer and Lusk suggested that glutamic acid might be oxidized on its β-carbon atom which on cleavage might yield serin, the latter being converted into glyceric acid on deamination. Glyceric acid, when given to the diabetic dog, was converted into glucose. Recently Dakin (9) has isolated a new amino-acid, β-hydroxyglutamic acid from caseinogen, and has also produced it synthetically. This acid, he finds, yields glucose to the extent of three of its carbon atoms when it is given to the diabetic dog.

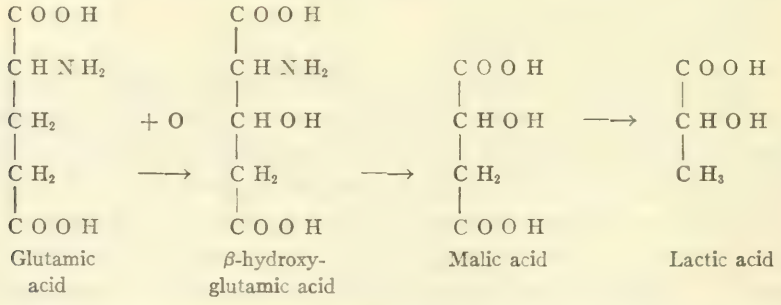
Perhaps the transformation of glutamic acid proceeds as follows:



Or since yeast cells may convert glutamic acid into ketoglutaric acid (29) and this again into succinic acid (11) and, since succinic acid if fed to the phlorhizinized dog, is convertible into glucose, (31a) the following intermediary reactions constitute a second possibility:



Dakin (9) believes that the metabolism of glutamic acid probably takes place through malic acid as an intermediate metabolite. Ringer, Frankel and Jones (31a) have shown that malic acid is convertible into glucose. Dakin's suggestion follows the formulae:



Whatever the intermediary reactions, the energy relations may be written as follows:

$$2C_5H_5NO_2 + 3H_2O + 3O_2 = C_6H_{12}O_6 + CN_2H_4O + 3H_2O + 3CO_2$$

Glutamic acid — Glucose — Urea

1 gram = 0.612 gram + 0.204 gram

3.662 calories = 2.298 calories + 0.516 calory

This reaction is therefore exothermic, 3.662 calories in glutamic acid yielding 2.298 calories in glucose, 0.516 calories in urea and 0.848 calories in the intermediary oxidative processes. The physio-

logically available calories in glutamic acid are 3.662 minus 0.516 contained in urea, or 3.146 per gram. Hence, in calculating the calories available one would say that 73 per cent of the total passed through the glucose stage and 27 per cent passed through other oxidative channels

If Rubner's theory (see p. 000) of specific dynamic action were correct, then glutamic acid would furnish energy to the cells in so far as it was convertible into glucose, whereas the rest of the energy content would be liberated as free heat. Its specific dynamic action could be measured as 27 per cent, which almost coincides with the figure 30 per cent, as given by Rubner. Since the protein of meat yields 22 per cent of glutamic acid and that of gliadin nearly 50 per cent (Osborne), it follows that an important fragment of protein metabolism is represented in this amino-acid.

However, it has been discovered that the ingestion of 20 grams of glutamic acid by a dog gives absolutely no specific dynamic action (22) and this is also true of its hypothetical cleavage product, succinic acid (3). The demonstration that glutamic acid exerted no specific dynamic action after its ingestion is a proof that the process of deamination and urea production have no influence upon the heat production.

It has furthermore been shown that aspartic acid, $HOO\text{-}CCH_2\text{-}CHNH_2\text{-}COOH$, exerts no specific dynamic action (3) and this further substantiates the above conclusions.

Other experiments showed that neither 20 grams of leucine nor 20 grams of tyrosine caused any conspicuous rise in metabolism after their ingestion (22), although tyrosine at least would present a multitudinous array of oxidative products.

It was only when two amino-acids which are completely converted into glucose by the diabetic organism were given, that the heat production of a normal dog was very greatly increased. These two amino-acids are glycocoll and alanin. Serin has never been tested but would probably behave like alanin. These experiments overthrow the validity of Rubner's theory of the specific dynamic action of protein.

In one experiment 20 grams of glycocoll were given to a dog and the metabolism rose 33.7 per cent above the basal level. The 20 grams of glycocoll contained 42 physiologically available calories of

which 34 calories or 81 per cent were available for metabolism between the second to the seventh hours in the calorimeter experiment after giving the substance. Since the heat production was increased by 33.75 calories, or by 80 per cent of the calories in the ingested substance, it is evident that the extra heat production after giving glycocoll may equal the entire energy which can be furnished by the metabolism of glycocoll itself.

This at once raises the question: Is the energy in glycocoll merely freed and given off without affecting the basal metabolism? Does it merely explode with a puff?

If one writes the reaction and the energy involved in the conversion of glycocoll into glucose and urea the following equation results:

$$6C_2H_4N_2O_5 + 3CO_2 + 3H_2O = 2C_6H_{12}O_6 + 3CH_4N_2O + 3O_2$$

Glycocoll	Glucose	Urea	Oxygen
20 grams	16 grams	8 grams	4.26 grams
62.2 cals.	60.08	20.22	14.0 as oxidized fat

According to this equation 62.2 calories in glycocoll become converted into glucose and urea, containing together 80.3 calories with the intermediary liberation of a compound yielding oxygen in such quantity that it can effect the oxidation of an amount of fat which can produce 14 calories. The reaction would therefore be rewritten as follows:

$$\text{Glycocoll} + \text{fat} + CO_2 + H_2O = \text{Glucose} + CH_4N_2O + CO_2 + H_2O$$

20 grams	= 16 gm. + 8 gm.
62.2 cals. + 14 cals.	= 60.08 cals. + 20.22 cals.

Hence, material containing 76.2 calories is converted into material containing 80.3 calories. The reaction is still *endothermic*.

When, however, glycocoll is given to a dog diabetic with phlorhizin the heat production is very greatly increased, far beyond the requirement of satisfying this endothermic quota of energy.

See following table for the results.

The extra calories produced over and above the basal metabolism for four hours amounted to 25.9 calories, which corresponds with 24.5 extra calories produced in the same dog when he was normal in the experiment already described.

Dog III, March 25, 1915, Experiment 104. Basal phlorhizin metabolism as affected by 20 grams of glycocoll in 210 cc. of water at 38° plus 1 gram of Liebig's extract

HOURS		R. Q.	CALORIES	
			Indirect	Direct
1	Basal	0.733	23.78	24.53
2	Basal	0.716	23.82	23.84
	Average	0.724	23.80	24.18
3	Glycocoll, 20 grams			
4	Glycocoll, 20 grams	0.707	34.21	32.34
5	Glycocoll, 20 grams	0.745	31.65	29.47
6	Glycocoll, 20 grams	0.700	29.24	30.07
7	Glycocoll, 20 grams	0.702	25.99	26.85
	Average	0.720	30.27	29.38

This is the *experimentum crusis* which demonstrates that the specific dynamic action of glycocoll is independent of its oxidation. Rather, there must be chemical intermediates produced which act upon the protoplasm of the cells, lifting them to a higher level of metabolism without it being necessary that they themselves furnish the energy of metabolism. I have therefore spoken of this condition as the *metabolism of amino-acid stimulation*. This does not necessarily mean that acid is actually liberated.

To investigate this point I have given to a dog 9.6 grams of glycocoll neutralized with 10 grams of sodium bicarbonate and have witnessed the heat production increase 5.2 calories per hour during the second and third hours. The bicarbonate given alone was without influence. When 7.6 grams of glycocoll acid were given the heat production rose 1.6 calories per hour and when 10 grams of glycollate of sodium were ingested a rise of only 1.2 calories was recorded. The administration of glycollic acid greatly reduced the carbon dioxide combining power of the blood, which testifies to its slow oxidation.

It would seem likely that glycollic acid would be the first intermediate product of glycocoll deamination, as follows:

$$\begin{array}{l} CH_2NH_2 \\ | \\ COOH \end{array} + HOH \longrightarrow \begin{array}{l} CH_2OH \\ | \\ COOH \end{array} + NH_3$$

However, glycollic acid is not convertible into glucose in the organism. It may be, however, that the reduction of the acid group takes place before or simultaneously with the deamination process and glycolaldehyde is generated, which substance it has been shown is convertible into glucose (39). If so, the stimulation of cellular metabolism probably occurs before this step because the synthetic production of glycogen does not involve a stimulation to increased heat production.

The experiments may possibly be explained after another fashion. It may be that the amino-acid is greedily absorbed by the cell and that the alkali neutralizing it is not. Under these circumstances the liberation of free acid may possibly be the stimulus which increases cellular metabolism. Under this hypothesis the cell membrane would be largely impermeable to the sodium salt of glycollic acid present in the blood after the ingestion of either the acid itself or glycollate of sodium and little result would be noticed in the way of cellular stimulation.

When glycocoll is given the extra heat production is proportional to the quantity ingested; that is to say, it is proportional to the intensity of the chemical stimulus.

When glycocoll is administered with glucose the extra heat production is the equivalent of the sum of the extra quantities of heat which either substance would have induced alone. Furthermore, when glucose and glycocoll are given at the height of fat ingestion the extra heat production rises to a level which is the equivalent of the influences exerted by the substances as individuals. This is seen in chart V and may be illustrated in the following table:

	HOURLY INCREASE IN CALORIES ABOVE BASAL	PER CENT
Glycocoll, 20 grams	4.9	25
Glucose, 70 grams	6.9	30
Fat, 75 grams	3.9	17
Sum of all	15.7	72
Glycocoll, 20 grams + glucose, 50 grams 4 hours after fat, 75 grams.	14.6	64

It is obvious that glycocoll, which is completely convertible into glucose, does not behave like glucose (1) in substituting its energy for the energy of glucose in metabolism; (2) in being passively elimi-

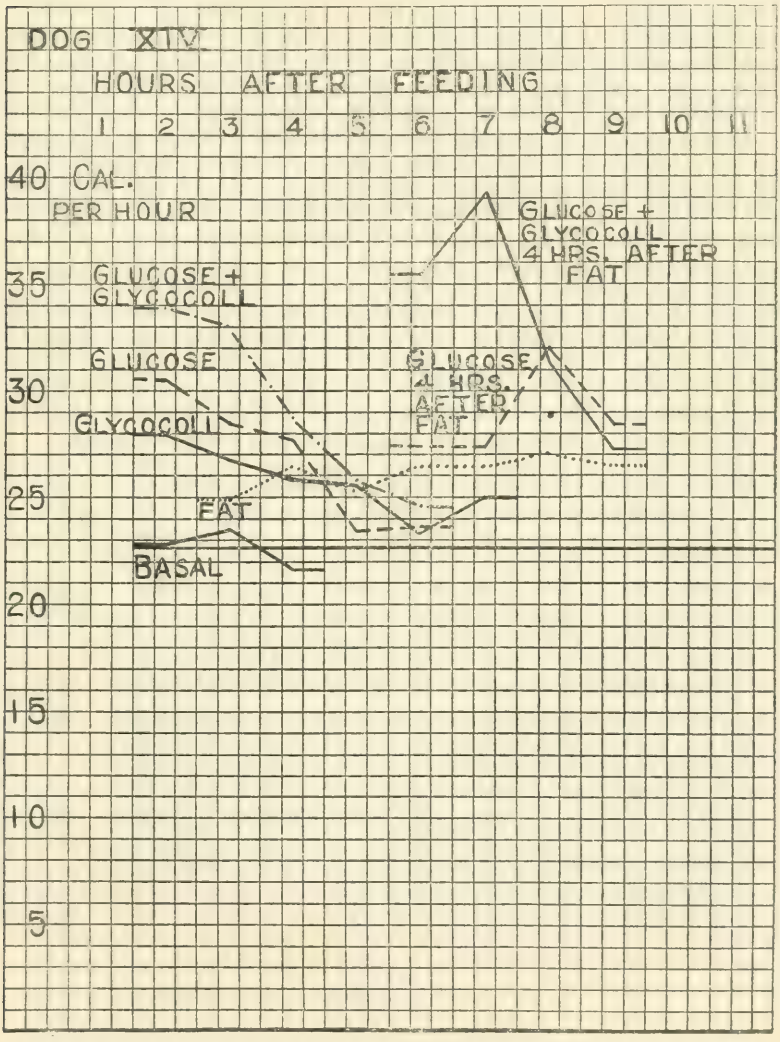


CHART V. THE EFFECT OF FAT, OF GLYCOCOLL, OF GLUCOSE, OF GLUCOSE PLUS GLYCOCOLL, AND OF GLUCOSE PLUS GLYCOCOLL PLUS FAT UPON THE HEAT PRODUCTION (28)

nated as glucose in the urine of the diabetic dog, It follows, also, that ingested glucose can not synthetically form glycocoll under normal conditions.

The behavior of alanin is in every way similar to that of glycocoll. It is completely convertible into glucose, perhaps through a lactic acid intermediary product. When given with glucose it does not replace glucose in metabolism but itself increases the metabolism by that quota which, acting alone, it would have induced. It stimulates to a higher heat production when given in phlorhizin glycosuria, though it is completely converted into glucose without undergoing oxidation in the process. Likewise, when given alone, it increases the basal level of metabolism upon which the energy for work is superimposed, while glucose molecules entering in large quantities have no power to augment the basal level of metabolism when the work done is accomplished at the expense of their energy content (see p. 330).. In this last factor the behavior of alanin is but characteristic of the whole complex of the protein molecule.

When lactic acid is given (33) to a dog there is quite an increase in the heat production and it seemed to the writer that this gave an explanation to the specific dynamic action of alanin. However, unpublished experiments show that lactic acid, when given with glucose, does not cause a summation in the extra heat production as transpires when glucose and alanin are given together (see p. 326). Hence, it appears likely that the specific dynamic action of alanin is dependent on a specific stimulus imparted to cellular protoplasm when after its absorption into the cell it suffers transformation into simpler substances. In all its reactions alanin resembles glycocoll except that its action is not quite as powerful per gram of substance metabolized. However, the evidence points to the fact that the specific dynamic action of the two substances is proportional to the number of molecules metabolized (21).

A. Summary

1. The extra heat which is the product of the specific dynamic action of protein may be used in substitution for the extra heat induced by the effect of environmental cold (Rubner).

2. The increase in heat production is proportional to the protein metabolism of the time. It occurs when endogenous protein metabolism increases as in the case of phlorhizin glycosuria (Rubner).

3. A dog given 1200 grams of meat showed a maximum increase in metabolism of 88 per cent above the basal metabolism, an increase which remained nearly at this height during the first ten hours after meat ingestion. Another dog, after taking 1000 grams of meat, showed an increase in metabolism of 93 per cent above the basal. These quantities of meat were approximately the maximum which the dogs would eat. Fifty per cent of the energy content of the increased protein metabolized appears in the form of heat of specific dynamic action.

4. When meat is thus given in excess of the nutritive needs of the cell there may be a retention of a part of the energy of the protein metabolized, deposited either in the form of glycogen or in the form of fat, depending upon the condition of the glycogen reservoirs of the body. Neither of these processes involves an appreciable liberation of energy.

5. In man the ingestion of 660 grams of meat caused a maximal rise in the basal metabolism of 46 per cent. Of the energy content of the increased protein metabolized 75 per cent appears in the form of the heat of the specific dynamic action.

6. If the energy required to accomplish a given quantity of work be determined before and after meat ingestion it is found that the energy requirement for work in the first instance is superimposed upon the metabolism as induced by the specific dynamic action of protein in the second instance. This strictly differentiates between the character of the specific dynamic action of protein and of glucose. In this regard alanin behaves exactly like protein and not like glucose.

7. Glutamic acid with its five carbon atoms exerts no specific dynamic action when given to a dog. The process of deamination and urea formation may therefore take place without increasing the heat production. Succinic acid, a possible intermediary metabolite, exerts no specific dynamic action.

8. Aspartic acid behaves like glutamic acid.

9. Neither leucin nor tyrosin cause a conspicuous rise in metabolism.

10. Administration of 20 grams of glycocoll to a normal dog causes

a very great increase in the heat production. The quantity of extra heat produced (25.9 calories in four hours) may amount to the entire energy of the glycocoll metabolized during the period.

11. When 20 grams of glycocoll were given to a dog diabetic with phlorhizin the quantity of extra heat produced in four hours (24.5 calories) was exactly the same as when the material was given to the same animal when normal in spite of the fact that the ingested glycocoll is completely converted into glucose and urea without oxidation. Therefore, some intermediary metabolites act as chemical stimuli to metabolism (Experimentum crucis).

12. Glycocoll neutralized with sodium bicarbonate has the same influence upon the heat production as when given alone. The bicarbonate given alone is without influence upon the metabolism.

13. Glycollic acid and sodium glycollate have little influence upon the heat production. It is indicated that glycollic acid may not be as readily permeable to cell membranes as is the readily diffusible glycocoll.

14. When glucose is given with glycocoll or when the two combined are given at the height of fat metabolism, the total specific dynamic action of the mixture is equal to the sum of those quantities of extra heat production which each substance acting separately would have induced. The calories of glycocoll can not, therefore, be substituted for the calories of glucose.

15. The behavior of alanin is analogous to that of glycocoll. Molecule for molecule, it exerts the same specific dynamic effect.

B. Conclusion

The specific dynamic action of protein consists in a specific chemical stimulus of the cellular protoplasm, which is independent of the oxidation of the material through which the stimulus is applied. It may be termed the *metabolism of amino-acid stimulation.*

V. A THEORY OF METABOLISM

It may be well to restate a theory of metabolism already advanced (23a) which is a modified form of one enunciated by Rubner (38).

One may conclude that the influence of food ingestion upon the

basal metabolism of the quiet, resting cell may be upon three independent mechanisms within the cell:

a. A mechanism which is receptive to a chemical stimulus derived from such amino-acids as glycocoll and alanin.

b. A mechanism of carbohydrate plethora which allows the metabolism of carbohydrate up to the limits imposed by "self regulation."

c. A mechanism capable of receiving power from that quota of fat which, when in excess, increases the heat production of the cell.

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HEMOLYTIC JAUNDICE

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INTRODUCTION

Definition

In general, any jaundice may be said to be hemolytic when it is due to increased destruction of the red blood cells, and not to obstruction of the bile passages. A good illustration is afforded by the jaundice which follows the transfusion of blood in cases where there is incompatibility between the patient's blood and that of the donor. Such a jaundice corresponds to the "hematogenous" jaundice of the older writers, a term which is again coming into use since Whipple

and Hooper (93) have shown that bile pigment may be formed outside of the liver and in the general circulation.

For the purposes of this article however, the term hemolytic jaundice will be restricted to a form of jaundice, usually chronic, in which diminished resistance of the red cells to hypotonic salt solutions is a conspicuous feature, while bile pigment is present in the stools and absent from the urine. Enlargement of the spleen and anemia complete the picture.

The disease occurs in two forms, the congenital and the acquired, the former being by far the commoner. The congenital type belongs to the inheritable diseases, occurring often in several successive generations, occasionally in several members of a family without cases among the ascendants, and also in a strictly congenital form, a single member of a family being affected from birth.

Synonyms

A great variety of names has been employed, according to different conceptions of the nature of the process, viz., chronic acholuric jaundice, chronic infectious jaundice with splenomegaly, chronic familial jaundice or cholemia, hemolytic splenomegaly, hemolytic anemia, and hemolytic jaundice. The last named, however, is the one almost universally used at present.

HISTORICAL

The recognition of the disease is of recent date. Imperfect accounts of the congenital form were given in 1885 by Murchison (65) and in 1890 by Wilson (103), but it was not until 1900 that the first accurate description was published by Minkowski (60). This was soon followed by articles in France by Gilbert, Castaigne and Lereboullet (32), and in England by Barlow and Shaw (4). Ten years later the condition was first recognized in America by Tileston and Griffin (85) and shortly afterwards by Thayer and Morris (83).

The nature of the disease was little understood till 1907, when Chauffard (14) discovered the significant fact that the red cells showed a markedly diminished resistance to hypotonic salt solutions. In the following year he reported (15) the presence of reticulated red cells in large numbers.

Widal (94) was the first, in 1907, to describe the acquired type in detail and recognize its hemolytic nature, though Hayem (39) had reported similar cases in 1898.

For these reasons the congenital form often is alluded to as the Minkowski-Chauffard type, and the acquired form as that of Hayem-Widal.

TYPES

I. THE CONGENITAL TYPE

The important features are as follows: Jaundice appears either at birth, or during childhood or youth, and persists throughout life. It is usually noted in more than one member of the family, and frequently in two, three, or even four generations. At times, however, though dating from birth, no other members of the family are affected. The icterus is not intense, there are no signs of obstruction of the bile ducts, and symptoms of cholemia, such as itching, bradycardia and xanthomata, are lacking. The urine shows the presence of urobilin, but no bile, while the stools are highly colored, and contain an excess of urobilin. Enlargement of the spleen, which may reach large proportions, is an almost constant feature, while the liver is only slightly or not at all enlarged. A moderate degree of anemia is the rule. The resistance of the red cells to hypotonic salt solutions is diminished, in marked contrast to the increased resistance met with in obstructive jaundice. Reticulated red cells are present in large numbers. The leucocytes may be either normal, increased, or decreased in number.

In spite of the long duration of the disease, the health does not suffer much, and many patients attain an advanced age, death being almost never due to the disease itself. As Chauffard has aptly remarked, the patients are rather jaundiced than sick. Except in a few cases, such as those of Weber (91) and Türk (87), the growth is not interfered with.

In the history a characteristic feature is the occurrence of the so-called "crises;" after an indiscretion of diet, a period of constipation, or without obvious cause, attacks take place in which there is repeated vomiting of bile, often accompanied by fever and pain

in the region of the spleen or liver. The jaundice deepens during these attacks, the spleen enlarges and if counts are made, it will be found that the red cells have diminished, often with great rapidity. These "crises of deglobulization," as they are termed by the French, occur more frequently in youth, diminishing in number and severity with advancing age.

Between attacks the patient feels fairly well. There is a marked tendency to nose-bleeds during childhood, but hemorrhages from other organs are not met with, an important distinction from Banti's disease and cirrhosis. The enlarged spleen often causes a sense of weight and oppression in the left hypochondrium, and pain may occur in this region, apart from "crises," as a result of perisplenitis.

Etiology

Heredity. The disease is often an exquisitely hereditary affection involving three or even four generations. It is transmitted equally by the male and by the female, and Wilson's (103) statement that it tends to pass from father to daughter, and from mother to son, does not hold good for most instances. The sexes are affected about equally. There seems to be no racial predisposition. Some of the children almost always escape, and the offspring of those who do, remain free from the affection. It has not been found possible to apply the Mendelian laws of the inheritance of dominant and recessive characters.

As in the case of other hereditary diseases, the etiology is obscure. Certain observers, notably Chauffard, attempt to ascribe the disease to hereditary syphilis and to tuberculosis. This seems the more plausible on account of the analogy of hemolytic jaundice with paroxysmal hemoglobinuria, a condition which is usually associated with inherited syphilis.

Chauffard (17) bases his argument on observations on a family in which the usual picture of hemolytic jaundice occurred in twins, the subjects of hereditary syphilis. The father was jaundiced from birth and showed a positive Wassermann reaction. Interesting phenomena were noted after injections of neosalvarsan. In all three splenic "crises" occurred, with pain and increased swelling of the spleen; in one of the twins there had been no previous crises.

The resistance of the red cells was decreased in two after the injection and increased in the other. The temporary appearance of isolysins was also noted. After a few injections these reactions appeared no longer.

Chauffard regards these phenomena as being in the nature of a Herxheimer reaction, or local reaction in the spleen due to the sudden liberation of toxins from spirochetes which have been killed by the drug. His observations, interesting as they are, cannot be said to prove his point, for he made no control tests on the effect of salvarsan injections in cases of hemolytic jaundice without syphilis, or in cases of syphilis without jaundice. Nor have syphilitic lesions ever been demonstrated in the spleen in hemolytic jaundice.

Guizzetti (38) has also reported a family in which hereditary syphilis is supposed to have played a part. Hemolytic jaundice occurred in four generations, and in two cases, brothers, a marked thickening of the frontal bone, claimed to be syphilitic, was found at autopsy. The husband in the first generation was said to have been syphilitic, but his wife, who was his first cousin, also suffered from splenomegaly, so that it is possible that syphilis had nothing to do with the jaundice transmitted to the offspring. It should be noted that in this family the disease ran a severe course, resulting in the early death of several members. Such malignancy has been noted in no other cases in the literature; it seems possible that it was due to the fact that both parents suffered from the disease, or that it was due to the complication with syphilis.

In general, however, the incidence of syphilis in hemolytic jaundice is not greater than in the population at large; thus Giffin (31) reports only one positive Wassermann reaction out of thirteen patients. Moreover, in the cases of the congenital type where active syphilis has existed, the employment of anti-syphilitic treatment has in no single instance resulted in a cure of the jaundice. It seems fair to conclude that syphilis is not of importance in the causation of the disease.

In the case of tuberculosis, the argument is even weaker. Apart from the casual occurrence of tuberculosis in these patients, it rests essentially on the result of tuberculin injections. It is again to Chauffard (17) that we owe observations on this point. In one

patient jaundice appeared at the age of fifteen during an attack of pleurisy with effusion. (The congenital type not infrequently first becomes manifest at this age after an acute infection.) When seen by Chauffard at the age of thirty there were signs of active tuberculosis at the left apex. An intradermal injection of tuberculin was followed by a marked local reaction, by pain and increased swelling of the spleen and increase in the jaundice. In another case, a man of twenty years, with a history of tuberculous peritonitis in infancy, still more striking events followed the intradermal injection of tuberculin. Besides an intense local reaction, there was fever of several days duration, the spleen doubled in size, the jaundice increased, acute anaemia supervened and the resistance decreased from 0.64 per cent to 0.76 per cent.

Chauffard considers these cases as showing a local reaction of the spleen to tuberculin, which he regards as proof of the tuberculous origin of the disease. According to him, hemolytic jaundice is a symptom, not a disease, with hereditary syphilis and tuberculosis as the most common factors. But as against this theory it may be objected, in the first place, that tuberculosis of the spleen has never been encountered in the numerous specimens examined, and secondly that hemolytic crises have often been reported in the congenital type in connection with acute infections of various sorts. Now a severe tuberculin reaction is certainly analogous to the toxemia produced by the acute infectious diseases. A verdict of "not proven" may therefore be returned in the case of tuberculosis also.

In conclusion it may be stated that the cause of congenital hemolytic jaundice remains to be discovered.

Pathogenesis

Any theory must take into account the increased fragility of the red cells and the splenomegaly. All writers are agreed that the jaundice is of hemolytic origin, as shown by the increased urobilin excretion (one molecule of hemoglobin gives rise to one molecule of bilirubin), the pigmentation of the organs, and probably certain of the blood changes.

Widal and his school believe that the primary factor is the decreased resistance, the abnormally fragile cells being destroyed in great

numbers by the normal hemolytic processes of the body, and the enlargement of the spleen being "spodogenous," or simply the result of the increased number of red cells destroyed there.

Troisier (86) on the other hand maintains that the primary condition is the formation of a hemolysin which becomes fixed in the red cells and renders them less resistant, and supports his view by the finding of hemolysins and decreased resistance of red cells in the pleural fluid in cases of hemothorax. Widal (97) accepts this view as applied to the acquired type, and believes that hemolysis does not occur in the circulating blood on account of a deficiency of complement.

Banti (2) however, was unable to demonstrate any lack of complement in the serum, and states that other observers have failed to find increased fragility in red cells that have fixed hemolysin. He believes that the primary fault lies in the spleen, and that hemolysins are produced in this organ in hemolytic jaudice. He states that he was able to reproduce the disease experimentally by the injection of hemolytic sera, observing after a single injection progressive anemia, with similar blood changes and decreased resistance. Both in normal animals and in those who had received injections, he observed that the splenic vein contained more hemoglobin in the serum than was found in other parts of the body, and that the fragility of the red corpuscles was also greater in the splenic vein. Two cases of splenectomy for hemolytic jaundice in man are said to have shown greater fragility in the splenic venous blood than in the peripheral circulation. He concludes that the spleen has an important hemolytic function and diminishes the resistance of the red cells which pass through it.

Banti believes that the pathogenesis of the disease in man is identical with that of his experimental anemia following injections of hemolytic sera, and assumes in the human disease the presence of substances, as yet unknown, which act on the spleen and cause it to produce hemolysins in excess.

Pearce (70, page 93), however, working with normal dogs, was unable to find any free hemoglobin in the serum of the splenic vein, and concludes that Banti's results were due to faulty technique. He found the resistance of the red cells usually the same in the splenic vein and in the artery, and only occasionally slightly less in the vein.

Since the corpuscles in the femoral vein were also at times less resistant he asks if the changes which have been found in the splenic vein are not those of venous blood in general.

In this connection the experimental studies of Joannovics and Pick (43) on toluylendiamin poisoning in dogs are of interest. They attempted to explain the fact that this substance is hemolytic *in vivo* but not *in vitro*. Following the lead offered by Faust and Tallqvist (28) who showed that the bothriocephalus latus contains oleic acid, a highly hemolytic substance, to which the anemia caused by this worm is probably due, they demonstrated in the livers of dogs poisoned with toluylendiamin the presence in large amounts of hemolytic substances of the nature of fatty acids. These were of two sorts: First, in dogs dying of very acute poisoning, a substance belonging to the fatty acids, but not oleic acid, and not associated with fatty metamorphosis in the liver, and the occurrence of which was not influenced by previous splenectomy; and second, in the more chronic cases, hemolytic higher and lower fatty acids, including oleic acid, associated with marked fatty changes in the liver. In these latter dogs, if a splenectomy was done previous to the poisoning, the amount of hemolysis shown by the liver extract was reduced to one-sixth of that of the controls, and very little fatty change was encountered in the liver. The authors also showed that proteins inhibit to a marked degree the hemolytic action of the unsaturated fatty acids.

The above results are of particular interest in view of the fact that touylenediamin poisoning leads to a condition strongly resembling hemolytic jaundice in man, with jaundice, anemia, enlargement of the spleen, and as Widal (95) has shown, increased fragility and numerous reticulated red cells.

Eppinger (27), King (47) and Medak (58) have worked along these lines in human pathology, and have reported in two cases of hemolytic jaundice a very high iodine number in the blood, indicating the presence of unsaturated fatty acids in excess. After splenectomy these patients showed a reduction of the iodine number to normal, along with other indications that the excessive hemolysis had ceased. These authors also found after splenectomy in normal dogs a decrease in the iodine number and an increase of the total fats of the blood and usually of the cholesterol.

Dubin and Pearce (25), however, were unable to confirm these findings in so far as they relate to dogs, and Csonka (22) has criticized the technic employed in determining the iodine number, and also the method of calculation. The results of Eppinger and his school are, therefore, in need of confirmation.

The part that cholesterol plays in hemolysis within the body remains obscure. While there is no doubt that free cholesterol inhibits hemolysis in the test-tube by saponin and many other hemolytic agents, the figures obtained from chemical analysis of the blood in our disease are conflicting, and even should they be consistently low, they would not indicate whether the lower protecting power of the serum against hemolysis were primary or secondary. Further study in this direction is needed.

The presence of hemolysins in the pathological spleen has not been demonstrated as yet. In four cases of splenectomy for hemolytic jaundice, those of Vaquez and Giroux (88) Antonelli (1), and two of Kahn (45) they have been looked for in vain.

However, the influence of the spleen on hemolysis in this disease is evidently very important, for after splenectomy a virtual cure is attained, with rapid disappearance of the jaundice, and return of the blood to normal so far as red count and morphology are concerned. The fact, on the other hand, that the diminished resistance almost always persists, is against the view that the primary fault lies in the spleen.

It is possible to explain the benefit derived from splenectomy without the hypothesis of abnormal formation of hemolysins in this organ. The extensive researches of Pearce and his associates (70) have shown that splenectomy in normal dogs results in a marked reduction in the hemolytic processes, so that jaundice is much more difficult to produce with hemolytic agents than in the unoperated animal. This is partly due to the fact that normally by far the greater part of hemolysis takes place in the spleen; after splenectomy the other portions of the hemolytic system, the lymph nodes, the stellate or Kupffer cells of the liver, and the bone marrow, are unable to compensate to any marked degree for the loss of the spleen. Partly it is due to a mechanical factor, as indicated in the work of Krumbhaar, Musser and Peet (49); the hemoglobin reaches the liver after splenec-

tomy in a more dilute form, because it comes by way of the general circulation instead of through the splenic vein. The liver is, therefore, able to handle the hemoglobin and to excrete it as bile pigment without the production of jaundice. A third factor in the difficulty of causing jaundice in the splenectomized is the increased resistance of the red cells which is uniformly present after removal of the spleen in the normal animal; apparently this does not hold good for hemolytic jaundice in man.

To sum up, our present knowledge indicates that the diminished resistance of the red cells is the leading factor in the causation of hemolytic jaundice in so far as the congenital type is concerned. It is possible that the same explanation applies to the acquired type also. Cases with normal resistance to hypotonic salt solutions might be accounted for by the assumption of abnormal fragility of a different sort, as indicated by the work of Hijmans van den Bergh (41), who demonstrated in his case increased fragility on exposure of the red cells to carbon dioxide. The spleen is a necessary link in the chain for the production of the other signs of the disease, and it is possible that its function is perverted, but that has not been proven as yet.

The pathology, diagnosis and treatment of the two types will be considered together.

Clinical picture

The jaundice. This is usually the first symptom noted, and may be present from birth, or first attract attention in childhood or early youth; exceptionally it does not occur until the age of 25, as in the case of Benjamin and Sluka (6). In well marked instances the sclerae are of a lemon-yellow color, and the skin of the body is distinctly yellow, while the face may be of a peculiar buff color which is quite characteristic. The greenish tint seen in long-standing complete obstruction of the bile ducts is never present. The jaundice may be so slight as to be apparent only on careful scrutiny. It varies in intensity from time to time, often being increased by fatigue, emotion, exposure to cold, during pregnancy, and particularly at the time of crises.

Exceptionally jaundice may be lacking, as in the family reported by Ward (89), in which the mother and maternal uncle showed mas-

sive splenomegaly and anemia, but no jaundice, while the child showed jaundice but no enlargement of the spleen. Götzky and Isaac (34) encountered a family in which the grandmother and father were jaundiced, while the three children were anemic with enlarged spleen and increased fragility, but no icterus. Occasionally, as in the family described by Poynton (74) the jaundice is recurrent, and between attacks there are anemia and splenic tumor without icterus.

The spleen. The presence of splenic tumor constitutes one of the most striking features of the disease. Its size corresponds roughly to the severity and duration of the condition; in well marked instances it reaches to the umbilicus or even to the lowest part of the abdomen. During the crises the spleen enlarges rapidly, and there is apt to be pain in the left hypochondrium. The splenic tumor is usually discovered after the jaundice, though in the case of Schlecht (81) it was noted two and one-half years before jaundice appeared, the child being under medical observation all this time.

In a few instances, otherwise typical, enlargement of the spleen has been lacking. It was so in two brothers and a sister reported by Pick (71), and in Pollak's (72) family, in which the mother, jaundiced since birth, showed no splenic tumor, although both of her daughters had large spleens.

The blood. A moderate anemia with counts varying from 3,000,000 to 4,500,000 is the rule, but in severe crises there may be a great destruction of red cells, as in Thursfield's case (84), with 1,000,000. Guinon, Rist and Simon (37) on the other hand have reported a case, the classification of which is doubtful, in which there were jaundice and splenomegaly, but the resistance was increased and there was a transitory polyglobulia of 7,600,000.

The hemoglobin is usually proportionately reduced, so that the color index is about one. In this respect the picture resembles pernicious anemia, but it has been suggested that the high hemoglobin reading is apparent rather than real, being due to the dark color of the serum. The average size of the red cells is usually decreased; there are considerable anisocytosis and polychromia, but poikilocytosis and stippling are unusual. Normoblasts are often present in small numbers, while megaloblasts are rarely met with.

The chief interest, however, lies in the decreased resistance of the red cells to various hemolyzing agents, but especially to hypotonic

salt solutions. This feature has been found in almost all of the reported cases, but like the other cardinal signs of this disease, it is occasionally lacking, as in the cases of Claus and Kalberlah (21), Lommel, (52) and Cade (12) while in that of Widal and Ravaut (101), the resistance was actually increased. It has been noted that the resistance may be normal at one time and decreased at another, especially during acute infections (Renaux, 75). In this connection the importance of technic should be emphasized, for if the sodium chloride is not thoroughly desiccated, too high figures will be obtained.

In most cases both the minimum and the maximum resistance are decreased, hemolysis often beginning at 0.60 per cent and being complete at 0.40 per cent, the normal figures being 0.44 to 0.48 per cent for the former, and 0.30 per cent for the latter. Sometimes only the minimum resistance is affected. Usually the results are the same with whole blood and with washed corpuscles, though some observers have found lower figures with the latter. For the technic the reader is referred to Pearce (70), page 273, and to Kolmer (48).

The resistance has also been found to be decreased to other hemolytic agents, such as anti-human hemolytic serum, cobra venom, and sometimes to saponin. Bittorf (9) showed that the resistance to acids was decreased; Grote (35) confirmed this and found the same to obtain for alkalies. Widal and others have noted that the red cells were hemolyzed by contact with normal sera, which did not hemolyze red cells derived from other persons.

Reticulation of the red cells is present to a degree met with in no other disease. This phenomenon consists in a net-work within the red cell, brought out by the so-called "vital" methods of staining, and especially well by brilliant cresyl-blue. This feature of hemolytic jaundice was first noted by Chauffard (15), who called it granular degeneration. This name should be dropped, as leading to confusion with the granular degeneration of Grawitz, or stippling, with which it has nothing to do. These reticulated or "skeined" cells occur in normal blood in small numbers, from 0.5 to 1 per cent, and in other forms of anemia up to about three per cent, while in hemolytic jaundice they make up from 10 to 20 per cent of the whole, and in the acquired type even up to 50 per cent. They are usually regarded as a sign of regeneration of the blood, as young cells that

have reached the circulation in an immature state. It has been suggested that they are less resistant than normal cells, but this has been found not to be the case.

The white cells show no constant variations, being usually normal in number, sometimes increased, and sometimes diminished. Some observers have noted a polynuclear leucocytosis at the time of crises, in contrast to the increased leucopenia which recurs at such times in pernicious anemia, but this is not a constant finding. The differential count is about normal, with a tendency toward increase of the polynuclears. Exceptionally a few myelocytes are seen. Lommel (52) reported a very unusual case in which myeloblasts were found during pregnancy in large numbers (65 per cent), but disappeared after the induction of abortion.

The serum is almost always highly colored, owing to the presence of bilirubin. Urobilin has usually been reported absent, but according to Guillain and Troisier (36) may be found if tested for by the delicate method of Grigaut. The freezing point has been found to be markedly lowered, which indicates an increased molecular concentration of the blood. Troisier (86) explains this as a result of diffusion of the salts of the red corpuscles into the plasma.

The presence of signs pointing to increased hemolysis naturally led to a search for hemolysins in the blood, but these have been found to be almost invariably absent in the congenital type. This subject will be dealt with more fully later, under the acquired type.

Hemagglutinins likewise are very rarely encountered.

The urine. The urine is high colored, owing to an increase of urochrome, the normal urinary pigment. Bile pigment is almost invariably absent, being noted only as a transitory phenomenon in some cases at the time of crises of deglobulization. Bile salts are also absent. Urobilin and urobilinogen on the other hand are very constantly present, being absent only in cases of slight intensity. Other pigments derived from hemoglobin, such as hematoporphyrin, are absent. Albumin and sugar are not found in uncomplicated cases.

The stools: The feces are never clay-colored, but as a rule are highly colored, and show quantitatively a marked increase of urobilin. For example, Eppinger (27) found in one case a total daily excretion of 3 grams, the normal being given as 0.15 gram. This he calculates

amounts to the destruction (and renovation) of the entire blood in the space of two days!

Metabolism. Complete studies have been made by McKelvy and Rosenbloom (54) by Goldschmidt, Pepper and Pearce (33), and by Denis (24). The fat metabolism was normal, both as regards absorption and fat-splitting. The elimination of iron was markedly increased; this is to be attributed, as is the increased urobilin excretion, to the excessive destruction of red cells. With regard to nitrogen, McKelvy and Rosenbloom found a negative balance, due, they believed, to a toxic destruction of protein, while Goldschmidt and Denis obtained positive balances.

The excretion of endogenous uric acid was found much increased by Tileston and Griffin (85), and high values were reported also by the above-mentioned writers and by Kahn (46).

McKelvy and Rosenbloom (55), in a second paper, reported a considerable loss of cholesterin in the feces, the output exceeding the intake by 7 grams in a five-day period.

The cholesterol of the blood is of interest, owing to the relation of this substance to hemolysis. According to Windaus (104), the inhibitory effect on hemolysis is exerted only by free cholesterol, not by the esters. The older publications are not of great value, owing to the lack of accurate methods. Chauffard, La Roche, and Grigaut (16) reported normal figures, as contrasted with an increase in obstructive jaundice. Studies by the more exact method of Windaus (105) and of Bloor (10) by which both free cholesterol and esters are determined, have been made in a few instances. Thus Medak (58) in one case found a low value for free cholesterol, which increased after splenectomy, mainly at the expense of the esters. King (47), however, reported a normal amount in his second case (his first case appears to have been the same patient as Medak's). In two unpublished cases studied by the writer no important variations from the normal were found.

Complications. The complication with cholelithiasis is so frequent that it might almost be considered a part of the disease. In no other condition do gall stones occur with such frequency, being present in 58 per cent of the cases operated on by W. J. Mayo (57). It is therefore natural to attribute the attacks of pain in the right

hypochondrium, which are of frequent occurrence, to this cause. Occasionally, however, attacks of hepatic pain occur in connection with crises, and may be due simply to the overloading of the liver with the products of blood destruction.

Gout has been reported by Murchison (65), in two of the families of Tileston and Griffin (85), and in a few other cases. While it may be only a coincidence, it is also possible that the long-continued increased uric acid production might be a factor predisposing to gout. The latter differs from hemolytic jaundice in that the elimination of uric acid is diminished instead of increased.

II. THE ACQUIRED TYPE

Classification

Acquired hemolytic jaundice is divided by the French writers into two groups: first, the cryptogenetic and second, the secondary. To these a third, the hemolysinic icterus of Chauffard and Vincent (19), is sometimes added.

Etiology

The cryptogenetic group, as the name implies, is of unknown causation. The secondary variety occurs in the course of a number of diseases, chiefly infections.

Syphilis. Cases of florid lues in the secondary stage, associated with the syndrome of hemolytic jaundice have been reported by Gaucher and Giroux (30), de Beurmann Bith and Cain (7), and by Nicolas (66). The resistance was decreased in all. The striking feature is that all were cured of their hemolytic jaundice by anti-syphilitic treatment. In the case of Sablé and Darrel (78) hereditary syphilis with active bone lesions was the cause of similar symptoms, which promptly disappeared under treatment with arsphenamin. These facts contrast strongly with the negative results obtained by anti-syphilitic treatment in cases of the congenital type in which syphilis is present.

Malaria. Sacquépée (79) and others have described cases of hemolytic jaundice appearing at the time of the acute attack in malaria, and cured by quinine; the type of parasite present was not

specified. Such cases present analogies with malarial hemoglobinuria or black-water fever.

Tuberculosis. Landouzy (50) has reported a case occuring in the "third stage" of this disease.

Other infections. The syndrome of hemolytic jaundice has been observed by Sacquépée (80) in connection with streptococcus septicemia, disappearing during convalescence. Lewin (51) found it dating from attacks of paratyphoid fever and dysentery, but in his cases the condition did not disappear with recovery from the acute infection, but became chronic. Widal, Lemierre and others (100) have described a remarkable case of septicemia due to the gas bacillus (B. aërogenes capsulatus) with hemoglobinemia and hemoglobinuria. In this case the hemolysis could be demonstrated as directly due to the action of a hemolysin secreted by the bacteria, for cultures hemolyzed blood very rapidly *in vitro*, a very exceptional phenomenon for this bacillus.

A case in which a toxic origin seems probable is that of Widal, Abrami and Brulé (98), in which the disease appeared following proctitis and ischio-rectal abscess, and got worse with the development of a stricture of the rectum; the hemolytic syndrome disappeared within a few days after the relief of the stricture by making an artificial anus. The patient remained well so long as the artificial anus functioned, but would have minor hemolytic attacks as soon as it became plugged.

Pregnancy. Roque, Chalier and Cordier (76) report a case associated with the toxemia of pregnancy. The usual signs of hemolytic jaundice were present, including diminished resistance and autoagglutination, and in addition there were multiple hemorrhages into the skin and mucous membranes. The patient was eight and one-half months pregnant and showed, as evidence of toxemia of pregnancy, general edema, amaurosis, neuroretinitis and albuminuria. Recovery ensued after the birth of a dead child.

Cirrhosis of the liver. The association with cirrhosis has been noted by Mouisset, Chalier and Nové-Josserand, (64), Chevallier and Tomkine (20) Eppinger (27) and a few others. Hemolytic jaundice occurs in both the periportal and the biliary types; the liver is almost always enlarged, and the spleen more so than is usual in ordinary cirrhosis.

It is to be regarded as a complication of the cirrhosis and is frequently a terminal event, being in that case usually associated with infectious processes and the hemorrhagic diethesis.

A remarkable case was reported by Mosse (62), in which there was marked polyglobulia with cyanosis, splenomegaly and acholuric jaundice. The resistance was not tested. The autopsy disclosed cirrhosis of the liver.

Carcinoma. Widal and Joltrain (99) observed hemolytic jaundice in a case of carcinoma of the bladder with abundant hematuria.

Leukemia. In Gaisböck's (29) case of acute lymphatic leukemia the hemolytic syndrome, with marked diminution in resistance, was a striking feature.

Pathogenesis

In the case of the secondary form, the pathogenesis is probably different from that of the congenital type. When it occurs in connection with acute infections, the condition may be due to the action of bacterial hemolysins, and in the other instances a toxic origin seems probable.

The pathogenesis of the idiopathic variety, however, is probably similar to that of the congenital form. There is one feature that differs and that required detailed discussion, namely the presence of hemolysins in the serum. This has been noted, almost exclusively in the acquired form, by a number of observers, chiefly French. They have been chiefly isolysins, i.e., the serum hemolyzes the red cells of other persons, but not those of the patient. This is an interesting observation, but hardly explains the occurrence of hemolysis in the patient. The value of this work is considerably impaired by the fact that isolysins have been found in normal persons, Moss (61) reporting them in no less than 23 per cent. Troisier (36), however, with the technic employed, found them in only 4 per cent of 125 cases of diseases other than hemolytic jaundice.

Chauffard and Vincent (19) have set up a separate type, the so-called hemolysinic icterus, in which isolysins are present in the serum, and the resistance of the red cells is normal: a fair number of cases coming within this category has been reported. On account however of the fact that intermediate forms are met with, showing both isoly-

sins and diminished resistance (Chauffard, Troisier and Girard, (18)), and because of the occurrence of isolysins in health, it seems best not to separate these cases.

The presence of autohemolysins on the other hand is always pathological. They have been reported in hemolytic icterus by three observers only. In the case of Chauffard and Vincent (19) in which there were hemaglobinuria and hemoglobinemia, there was slight additional hemolysis on mixing the patients serum with his own corpuscles. In view of the fact that clear serum could not be obtained for the test, there is a possibility of error.

Roth (77) reported an interesting phenomenon in a case of pernicious anemia, in which autolysins were apparently present. It was found however that the patient's red cells were hemolyzed by the sera of fifty other patients, some of which sera were hemolytic only for the red cells of the patient. He concludes that the hemolysis was due not to the presence of autolysin, but to injury to the red corpuscles, so that hemolysis occurred with the isolysins which are probably present to a greater or less degree in all sera. He points out that these tests were not made in the case of Chauffard and Vincent.

Beckmann (5), however, reported two cases (one congenital and one acquired) in which the objection of Roth was met. The hemolysis however, was but slight, so that there is a possibility of an error in technic.

Lüdke (53) has recently published some interesting observations, which if confirmed, would go far to establish the rôle of hemolysins in hemolytic jaundice. Out of four cases (two of each variety) he found autolysins present in two (one congenital, one acquired), but only during crises. Both of these cases showed slight hemaglobinuria during crises. All four showed the presence of isolysins. The test was made by mixing the patient's clear serum with the patient's washed corpuscles and adding complement (amount and kind not stated). The fact that autolysins were found during crises, but were regularly absent during the intervals, would seem to point to some causal relationship between the two.

Lüdke was apparently able to obtain experimental confirmation of his findings. He made dogs anemic by bleeding and then injecting red corpuscles from the same dog. After a single injection both

auto and isolysins appeared in nine of eleven experiments. The splenic extracts of such dogs showed a strong hemolytic action on their own corpuscles. The splenic extract from dogs showing the presence of hemolysins, when injected intravenously into healthy dogs, caused a marked anemia with diminished resistance, while the extract of spleens from healthy dogs had no such effect. He concludes from these experiments that hemolysins may be elaborated in the spleen.

It is impossible to form a judgment of Lüdke's work without further details, which he promises to supply in a later publication. It should be noted however, that his cases were peculiar in that the Donath-Landsteiner test was positive in both, while other observers have found this test constantly negative. The demonstration of autolysins is difficult, and a standard technic has not yet been developed.

Hemagglutinins. Isoagglutinins have been shown in some cases of both types. Since, however, no attention has been paid to the presence of normal agglutinins, which Moss (61) has shown to be present in 89 per cent of healthy individuals, this work is without value. It is much to be desired that in future the agglutination-group to which the patient belongs should be determined, according to the method of Moss.

The presence of *autoagglutinins*, however, is always pathological, and is rarely met with outside of hemolytic jaundice. It has considerable theoretical as well as practical importance, since agglutination is considered by many to be a preliminary step in the process of hemolysis.

Clinical picture

The acquired type is much less frequent than the congenital, and as described by Widal (96) differs from it in several important respects.

The clinical course is more severe, ending not uncommonly in death. The anemia is more marked, the average red count according to Krumbhaar (70, page 258) being 2,000,000, against 3,300,000 for the congenital form. Counts of 1,000,000 or below are no rareties. The crises of deglobulization are more marked, and give to the disease a very chequered picture. The regeneration is at times extraordinarily rapid, as in Pollitzer's case (73), where the count rose in thirty days from 640,000 to 4,000,000. The jaundice is often less marked than in the congenital type and may be lacking.

The resistance of the red cells is less constantly diminished, and to a lesser degree. Widal states that in this type the resistance is normal with whole blood, and diminished with washed corpuscles, but further experience has shown that this does not always obtain. Hijmans van den Bergh (41) has described an interesting case in which the resistance was normal to salt solution, but hemolysis occurred if a mixture of the patient's corpuscles and normal serum was placed in an atmosphere of carbon dioxide. The same occurred with a mixture of the patient's corpuscles and his own serum, but never in the case of normal corpuscles. He concludes that a special form of fragility was present.

Widal, Abrami and Brulé (96) have described the presence of a phenomenon, auto-agglutination of the red cells, which is almost constantly absent in the congenital type. Lüdke (53) alone has reported its occurrence in the latter. It is tested for by mixing in a watch glass one drop of the patient's corpuscles with ten drops of his own serum, and letting the mixture stand fifteen minutes at room temperature. The red cells become agglutinated into a dense pedicle which cannot be broken up by shaking. The results may be confirmed by microscopical examination. They state that auto-agglutination was present in all their acquired cases, but never in the congenital type, or in other diseases. Other authors, however, have reported less constant results, e.g., Biffis (8) found the test positive in only one of five cases.

There are in the literature a number of border-line cases between acquired hemolytic jaundice and pernicious anemia, such as those of Widal and Weissenbach (102) Weber (90) and case II of Biffis. Here with diminished fragility of the red cells and jaundice, some or all of the signs of pernicious anemia were present, and it is a question whether they should be classified as pernicious anemia with jaundice, or as a pernicious type of hemolytic jaundice. It should be noted that in pernicious anemia the resistance is almost always normal or increased. The writer has recently encountered a similar case (unpublished) in which, with increased fragility there was a rapidly progressive fatal anemia, without jaundice. The color index was low and the average diameter of the red cells not increased, normoblasts exceeded megaloblasts in number, but the autopsy disclosed a

megaloblastic bone marrow and blood-forming foci in the liver and spleen.

Another variation from the usual type has been reported quite often, in which hemaglobinuria is a prominent feature. This may occur over long periods of time, as in case V of Biffis, or in a fulminating manner, as in that of Chauffard and Vincent (19). The Donath-Landsteiner test was negative in all. Hemoglobin was usually detected in the serum also.

An acute case of acquired hemolytic jaundice has been described by Gaisböck (29). A man twenty-two years old was seized acutely with high fever and rapidly progressive anemia, with death at the end of six weeks, after a single remission. There was constant though slight icterus; the spleen was not enlarged, except slightly during the remission. The blood showed the following signs: The red count sank to 500,000; the color index varied between 0.6 and 1.3; there was microcytosis with numerous normoblasts; leucopenia was present. The minimum resistance was much decreased while the maximum was increased. The autopsy showed a normoblastic bonemarrow, and blood-forming foci in the liver and spleen with increased pigment in the latter. Such a case may be considered as simply a more malignant form of the disease, in which death has occurred early during a crisis of deglobulization.

The question of the unity of the two types (congenital and acquired) may be considered at this point. In favor of the view which regards the two as separate entities may be advanced (*a*) the different clinical picture (*b*) the different age of onset (*c*) the lack of familial or hereditary influences, (*d*) the different etiology. As regards the first point, it should be noted that a number of congenital cases have been reported that have resembled clinically the acquired type, with grave crises and very low blood counts, while on the other hand some acquired cases, like these of Biffis (8) have shown an ever course without periodic attacks, thus resembling the congenital type. The more marked fragility in the congenital type is by no means a constant difference, and even the presence of autoagglutination has been noted, though rarely, in the congenital type, as by Lüdke (53).

The resemblance of the clinical picture in the two types may be so strong that cases reported at first as acquired have been shown later,

by the discovery of cases among the relatives, to belong to the congenital group, as in Hayem's case (40). In one of Giffin's cases (31) the finding of increased fragility in the mother, though she was free from symptoms, was the only sign leading to the correct interpretation.

The age at onset is an unreliable criterion, it being by no means uncommon to have the congenital type begin in the second decade or even somewhat later. Cases beginning after thirty, however, and these form a minority of the cases reported as acquired, apparently never show any evidence of a hereditary factor.

The third point, the lack of hereditary influences, is not of much value as a distinguishing sign. For many of the hereditary diseases, such as progressive muscular dystrophy, occur at times in only one member of a family. The fact, however, that in cases of the acquired type recovery may occur constitutes an important difference.

The most valid reason, however, for separating the two types appears to rest in the etiology. For while the cause of the congenital type remains obscure, in many of the acquired cases the treatment of some associated condition, such as lues, malaria, a stricture of the intestine, has resulted in a cure of the jaundice. This is never the case in the congenital type, even in those rare cases accompanied by hereditary syphilis.

To sum up, it is best for the present to distinguish a congenital and an acquired type. But it will be safer to consider all cases as congenital unless it can be shown that they belong to the secondary group, with undoubted relation to some infection, intoxication, or malignant disease, or unless they begin late in life, after the third decade.

PATHOLOGY OF HEMOLYTIC JAUNDICE

Our knowledge of the pathology has been derived partly from autopsy reports, partly from the examination of excised spleens. Since no differences have been found between the congenital and the acquired types, the two may be considered together.

The spleen. The gross appearances are as follows: The organ is greatly enlarged, the average weight of 12 excised spleens being 1070 grams according to Giffin, (31), and of nine spleens at autopsy 716

grams. The capsule is often thickened and there may be adhesions to the diaphragm, both the result of old perisplenitis. The trabeculae are not thickened, the follicles appear few and small. The striking thing is the marked engorgement with blood, Guizzetti (38) remarking that the organ became reduced to one third its former size after the blood was squeezed out. Infarction has been noted in a few cases, in the absence of heart disease.

On microscopic examination the most striking thing is the marked congestion. This may be general, but often it is confined to the pulp (or "cords of Billroth"), the sinuses being empty. This peculiar distribution of the congestion was first noted by Vaquez and Giroux (88). It is unusual in other conditions; in chronic passive hyperemia for example the sinuses are engorged.

The trabeculae and reticulum show no marked degree of thickening. This constitutes an important point of distinction from Banti's disease.

The follicles appear fewer because they are widely separated owing to the congestion. They are usually normal except for the condition of the follicular arterioles, which often show a hyaline thickening, as described by Guizzetti (38), Sisto (82) and others. This change may be found also in the arterioles of the pulp, but to a lesser degree. A moderate degree of fibrosis of the follicles is sometimes encountered.

Pigment is present in the organ in varying amounts, being often very abundant, at other times scanty, or even absent, as in the case of Goldschmidt, Pepper and Pearce (33). It is chiefly within endothelial cells in the sinuses, and usually gives the iron reaction. The amount of pigment does not depend entirely on the duration of the disease, for Elliott and Kanavel (26) found very little in a man of fifty-seven years, jaundiced since birth. Phagocytosis of red cells is sometimes observed. The endothelial cells lining the sinuses may be changed from the normal flat type to an oval shape, as noted by Guizzetti and Sisto.

Liver. The size is about normal. There are no signs of cirrhosis, except in the rare cases of acquired hemolytic jaundice secondary to cirrhosis. The bile ducts are always normal, except where changes due to gall stones have occurred, as in Sisto's second case (82) with marked cholangitis and calculi in the common duct, and in the second

case of Tileston and Giffin (85). There is no deposit of bile pigment in the liver cells. Pigmentation to a greater or less degree is the rule, being absent only in the case of Marchiafava and Nazzari (56). It may be so abundant as to compare with that of hemachromotosis; as in an unpublished case recently seen by the writer. The pigment occurs in the form of coarse brownish granules, which usually give the iron reaction. It is situated mostly in the hepatic cells, especially at the periphery of the lobules, and in the stellate or "Kupffer" cells, though some may occur in the periportal spaces. Otherwise there are no changes, except those due to intercurrent diseases. Gall stones are present in a little over 50 per cent of the cases.

Bone marrow. The bone marrow of the long bones has been found red and in a very active state, with numerous normoblasts and myelocytes, in all the cases, with the exception of case II of Sisto, in which the anemia was not marked. Pigmentation is not noted in the records.

The lymph nodes. Pigmentation has been found in a few instances; in the writer's unpublished case it was extreme, the pigment being within endothelial cells in the sinuses and giving the iron reaction. Three cases have shown the change to hemolymph nodes, with congestion, phagocytosis of red cells and pigmentation.

Kidneys. There was a very marked siderosis in the case of Minkowski (60), who isolated $\frac{1}{2}$ gram of iron from one kidney; also in the case of Marchiafava and Nazzari (56), and to a lesser degree in that of Oettinger (67). The pigment is chiefly deposited in the convoluted tubules. In Marchiafava's case the pigmentation was exclusively confined to the kidneys, and the urine showed casts containing hemaglobin. This variation in the place of deposition of the pigment is interesting, suggesting that in such cases the hemaglobin is set free in the general circulation and reaches the kidneys, while as a rule the hemolysis takes place in the spleen and the pigment is deposited here, or is transported to the liver.

To sum up, the spleen shows marked congestion, often of a peculiar sort, involving the pulp but not the sinuses. The reticuloendothelial apparatus, as Aschoff calls it, namely the endothelial cells of the spleen, liver, bone marrow and lymph nodes, shows signs

of hemolytic activity, such as phagocytosis of red cells and pigment deposit. The bone marrow shows the usual change from fatty to red marrow, as met with in most severe anemias.

DIFFERENTIAL DIAGNOSIS

Since most of the cases belong to the congenital type, a careful history, with special inquiry into the occurrence of jaundice among the relatives is of the greatest importance. The history of crises with pain and anemia is very suggestive. Any case of chronic non-obstructive jaundice, with or without enlargement of the spleen, should have the resistance of the red cells tested, and if this is lowered, the diagnosis of hemolytic jaundice is practically certain. If the resistance is normal, this does not exclude the diagnosis, provided the picture is otherwise typical. The resistance should also be tested where there is chronic anemia with splenomegaly, because hemolytic anemia without jaundice sometimes occurs. The presence of a considerable number of reticulated red cells, e.g., over 4 per cent, is valuable confirmatory evidence. The other important signs are anemia, increased urobilin excretion, the absence of bile pigment in the urine, highly colored stools and splenomegaly. Occasionally, however, any one of the above signs may be absent, and the diagnosis must rest upon the clinical picture as a whole.

In general, the diagnosis is to be made from other diseases accompanied by jaundice, diseases with splenomegaly and diseases with anemia.

1. Diseases with jaundice

Obstructive jaundice. This is excluded by the increased urobilin content and absence of decoloration of the feces, by the absence of bile pigment and bile salts from the urine, and by the absence of fatty stools. The resistance of the red cells is increased rather than diminished in obstructive jaundice.

Cholelithiasis. This is the most frequent source of error in diagnosis, owing to the fact that no less than sixty per cent of the cases of hemolytic jaundice are complicated by gall-stones. Many patients have undergone operation on the gall bladder, under the mistaken belief that the jaundice was due to calculi. It should be

borne in mind that in disease of the gall bladder, jaundice, if present, is of the obstructive variety, and that splenic tumor is absent unless cholangitis complicates the picture, and even then is of only moderate proportions.

Acute infectious diseases with jaundice. In yellow fever and spirochetal jaundice, icterus constitutes the most striking feature. In pneumonia and streptococcal septicemia, jaundice is not infrequent. In all of these diseases it is probably hemolytic in origin. Since in such cases it is purely symptomatic, it does not require further discussion here.

Familial icterus of the new-born. This is a very rare disease, in which several children of a family are seized with deep jaundice shortly after birth, and usually die within a few days with hemorrhages and cerebral symptoms. The etiology is obscure. In the exceptional cases of recovery the jaundice disappears, so that confusion with hemolytic jaundice should not arise. It is not an hereditary disease.

2. Diseases with splenomegaly

Only those diseases associated with chronic enlargement come into question.

Banti's disease. This name is employed instead of splenic anemia as being more precise. Many cases of hemolytic jaundice have been mistaken for Banti's disease, for the two have several points in common. Banti's disease in the early stage is excluded by the presence of jaundice and of lessened resistance of the red cells, and in the later stage by the absence of indications of cirrhosis of the liver. Reticulated red cells are not abundant in Banti's disease. The occurrence of other cases in the family clinches the diagnosis of hemolytic jaundice.

Gaucher's disease, or large-celled splenomegaly. This rare disease tends to occur in several members of a family, usually the females, but is never hereditary. There is a yellowish discoloration of the skin, but true jaundice is lacking, and so far as known, the resistance of the red cells is normal. The spleen is enormously enlarged, and the liver considerably. A moderate anemia of the secondary type is present. Brill and Mandlebaum (11) have called attention to a yellowish wedge-shaped thickening of the conjunctivae, seen on both sides of the cornea, which they regard as diagnostic.

Syphilis. Syphilis of the liver may be accompanied by great enlargement of the spleen, but jaundice is rare. The clinical picture may resemble that of Banti's disease so closely, that the diagnosis is made only at the autopsy-table. Occasionally, as noted above, both the acquired and the hereditary forms of lues may lead to true hemolytic jaundice of the acquired type, which is curable by anti-syphilitic treatment. Or again, syphilis, either acquired or hereditary, may occur as an accidental complication of the congenital type of jaundice. In such cases the finding of a positive Wassermann reaction may be misleading, but the results of a resistance test, of anti-syphilitic treatment, and the possible occurrence of jaundice in other members of the family will lead to a correct diagnosis.

Cirrhosis of the liver. The late stage of this disease is readily excluded by the absence of ascites, of signs of collateral circulation and of hemorrhage. The early stages of cirrhosis do not show much enlargement of the spleen, nor jaundice, except in the Hanot's type, where the liver is much enlarged, while in hemolytic jaundice the size is normal or only moderately increased. There is a rare juvenile form of cirrhosis, described by Jollye (44) and others, which may be familial and hence lead to difficulty. The growth is stunted, the liver is greatly enlarged and presents the lesions of biliary cirrhosis. The jaundice is of the obstructive type, the resistance presumably increased, and ascites occurs as a late feature; these points will suffice for diagnosis.

In cases of cirrhosis with an unusual degree of splenic enlargement, the possibility of a superadded hemolytic jaundice should be borne in mind, and the resistance of the red cells and the urobilin excretion measured.

Malaria. The spleen may be greatly enlarged in chronic malaria, but in the absence of acute attacks, there is no jaundice. As already noted, the syndrome of hemolytic jaundice has been observed occasionally in connection with acute malaria, in which case plasmodia can be found in the blood.

Tropical diseases with splenomegaly. Kala-azar has in common with hemolytic jaundice the splenomegaly and the anemia. There is no jaundice. Periods of fever alternate with periods of normal temperature. There are marked leucopenia and lymphocytosis. A

positive diagnosis is made by finding the causative organism, Leishmania Donovani, in material obtained by puncture of the liver or spleen. There is also, according to Castellani and Chalmers (13) a form of tropical splenomegaly not due to this parasite, which resembles Banti's disease, but is distinguished from it by the occurrence of irregular attacks of fever.

Leukemia. The examination of the blood will suffice for diagnosis. Very rarely the occurrence of the hemolytic syndrome has been noted in this disease.

Hodgkin's disease. The spleen is often much enlarged, but in the ordinary form the marked enlargement of the lymph nodes and the absence of jaundice render confusion with hemolytic jaundice unlikely. Very rarely, however, in Hodgkin's disease, there is splenomegaly without involvement of the peripheral lymph nodes, the abdominal nodes alone being affected. In such a case jaundice may occur from pressure on the bile passages by an enlarged node; the obstructive character of the juandice and the absence of diminished resistance are sufficient to exclude hemolytic jaundice.

Polycythemia. In this disease the increased number of red cells is in marked contrast to the anemia of hemolytic jaundice. The spleen is usually considerably enlarged, but jaundice is rare. Confusion could occur only in the very exceptional borderline cases, or in the end stage of polycythemia, when there may be anemia, sometimes combined with a leukemic blood picture.

Diseases of infancy with splenomegaly. Difficulty need arise only in regard to sporadic cases of hemolytic jaundice, in which no other members of the family are affected. The so-called Von Jaksch disease and the enlarged spleen of rickets and tuberculosis are readily differentiated by the absence of jaundice. Hereditary syphilis, however, sometimes leads to icterus, and here it may be necessary to resort to a test of the resistance of the red cells as well as the Wassermann reaction, on account of the occasional association of the two diseases. In congenital obliteration of the bile ducts jaundice is intense and of the obstructive type, and therefore easily distinguished. In sepsis of the new born the presence of fever and the almost inevitable fatal outcome are distinguishing features; it should be remembered that septicemia may be, though, rarely, accompanied by the hemolytic syndrome.

3. Diseases with anemia

Pernicious anemia is the only form that may give rise to diagnostic difficulties, and then only in the case of the acquired type of hemolytic jaundice. As already noted, a few cases occur in which it is a mere matter of opinion whether they should be classified as pernicious anemia with jaundice, or as a pernicious type of hemolytic jaundice. The resistance in pernicious anemia is usually increased, but occasionally it is diminished, as noted by Hill (42).

TREATMENT

Medical treatment

It goes without saying that all the usual methods of treatment for anemia have been tried, especially iron and arsenic. Though Widal speaks warmly of the long-continued administration of iron in the acquired type, it should be remembered that spontaneous remissions are frequent in this disease, and other writers have not noticed much benefit from this drug. The use of arsenic has also been without effect, except in those cases of the acquired type associated with active syphilis. In the congenital type of hemolytic jaundice, where hereditary syphilis is associated, no cure of the jaundice is to be expected from anti-syphilitic treatment, though some improvement in the general condition of the patient may result.

The fact that cholesterol in the test-tube inhibits hemolysis has lead to the administration of this substance. Parisot and Heully (69) noted a marked temporary improvement in the general condition, with some diminution in the jaundice and anemia, cessation of the painful crises, and increase of the resistance. Oulmont and Boidin (68) gave it to a patient with the acquired type showing diminished cholesterol in the blood, and noted that the cholesterol increased to a normal figure and the resistance also increased, but the jaundice remained unaffected. As was to be expected the effect was only temporary, ceasing as soon as the drug was stopped.

Treatment by means of the Röntgen rays has been practised by Barjon (3), Mosse (63) and others, with the result that the spleen has decreased somewhat in size, but the other signs of the disease have persisted. It is therefore not to be recommended.

Surgical treatment

The importance of the spleen as a factor in hemolysis, and the marked enlargement of the organ, soon led to the attempt to cure the disease by removal of the spleen. The operation of splenectomy for hemolytic jaundice was first performed in the case of Vaquez and Giroux (88) and ended fatally. In 1911, however, Micheli (59) removed the spleen in a case of the acquired type with brilliant results, amounting apparently to a cure. Since then the operation has been performed with increasing frequency and most happy consequences. The jaundice disappears within a few days, and does not return. The red count rises to a normal figure, usually within a few weeks, and the urobilin excretion rapidly drops to normal, indicating a cessation of the excessive hemolysis. The lower resistance of the red cells, however, usually persists. Thus Dawson (23) reports abnormal fragility of the red cells in a patient, otherwise healthy, whose spleen had been removed twenty-seven years previously by Spencer Wells. In a few cases, however, as in that of Thursfield (84), the resistance has risen to normal and remained there.

The case of Whipham (92) has been cited as one of failure of splenectomy to cure. It occurred in a girl of six, with negative family history. The spleen was greatly enlarged and there was progressive anemia, with a red count under one million. The operation resulted in great improvement in the condition, with a return of the resistance to normal, and of the red cells to above normal (6,000,000). Three months later, however, the jaundice returned, and death occurred in a few days, without marked anemia. There was no autopsy. The intensity of the jaundice, which is described as a deep olive-green, and the fact that bile pigment was constantly present in the urine, renders this case very atypical, with a strong probability of organic disease of the liver. The case can be excluded on the ground that it was not one of pure hemolytic jaundice.

In the congenital type, a permanent cure may be predicted. Thus in Giffin's (31) series, reported from the Mayo clinic, all but one of ten patients reported themselves as well at periods up to five years after operation, and the remaining case was an atypical one of the acquired type, with probable biliary cirrhosis and a blood picture like that of pernicious anemia. Also in cases of the acquired

type, unless they are secondary to grave and incurable disease (cirrhosis, carcinoma, etc.) the prospects for cure are excellent.

The immediate mortality, high in earlier cases, has been greatly reduced, so that Mayo (57) was able to report nineteen operations with but one death (5.3 per cent). This has been accomplished partly by improvement in technic, partly by the transfusion of blood before, and also afterwards if much blood has been lost.

The operation is therefore to be recommended in the congenital type if the symptoms are sufficiently severe, and in the "primary" cases of the acquired type. Where the condition is secondary to other disease, each case will have to be decided on its merits, bearing in mind that splenectomy will almost certainly decrease the hemolysis, but will not influence organic disease in other parts of the body.

The question of an operation for gall stones often arises in these patients. It is probably best to do the splenectomy first, and if the condition of the patient permits, to remove the gall stones at the same operation. This was successfully accomplished in a case recently studied by the writer. The removal of the spleen alone usually does not suffice, the attacks of biliary colic recurring after the operation.

PROGNOSIS

In the congenital type the prognosis is good as to life, there being almost no instances of death from the disease itself. But the frequent complication by gall-stones, the chronic anemia and crises of deglobulization, make the condition of many of these patients more or less miserable. Usually as old age approaches, the anemia becomes less and crises rarer, but apart from operative measures, this is the most that can be held out to the sufferer, for the condition persists throughout life. The brilliant effects of splenectomy have been considered above.

The prognosis in the acquired type is less favorable, death in many instances resulting directly from the anemia or from intercurrent infections. Recovery may occur spontaneously, but is not the rule. The course is in general more severe than in the congenital type, and the patient is usually incapacitated for work for long periods. The operation of splenectomy offers excellent chances for cure in the primary or cryptogenetic form, except in the cases bordering on pernicious anemia.

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A BACTERIOLOGICAL AND CLINICAL CONSIDERATION OF BACILLARY DYSENTERY IN ADULTS AND CHILDREN

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I. INTRODUCTION*

The term dysentery (Δυσεντερια) (bowel trouble) was introduced by Hippocrates (1) to denote a condition characterized by the frequent passage of stools containing blood and mucus, accompanied by straining and tenesmus. Some of the cases that were described at that time (1) were doubtless amebic in origin for the occurrence of liver complications is mentioned. The outbreak in Xerxes' army during the Grecian campaign in 480 B.C. (2), however, was very likely bacillary.

Not until the discovery of the ameba histolytica and B. dysenteriae at the end of the last century could epidemics of bacillary dysentery be accurately differentiated from those of the amebic variety. Only by noting the absence of liver complications in the older chronicles can it be assumed that bacillary dysentery was the type described, and even then one is not always justified in so doing, for other infectious processes in the intestinal tract (paratyphoid-Gaertner group) may occasionally present a clinical picture similar to bacillary dysentery. It is now well known that large single abscesses of the liver complicate only the amebic form of the disease while even multiple small pyemic abscesses are rare in bacillary dysentery. Rogers (3) states that the conditions under which dysentery occurs may be of assistance in determining the type of the disease. "Epidemic dysentery in asylums, jails or in long occupied and unsanitary military camps during war is nearly certain to be bacillary, while sporadic cases in a warm climate are more frequently amebic."

*I am indebted to Hirsch (4), Kartulis (5), Rogers (3), Gettings (6), Castellani and Chalmers (7) for many historical details.

Dysentery among the civilian population (historical date)

Epidemics of dysentery prior to the time of Hippocrates cannot be differentiated into amebic and bacillary varieties. The disease is mentioned in Papyrus Ebers (8). Atisar is its name in the older commentaries of British India (9). Although acute and chronic types of dysentery were mentioned, hepatic complications are not recorded. Probably amebic and bacillary types were considered together for both occur in India (10, 11, 12). The etiology of the cases of dysentery described by Aretaeus (13), Celsus (14), Archigenes (15), Caius Arelianus (16) and Avicenna (17) is doubtful. The outbreaks noted in Europe throughout the middle ages (18, 19, 20, 21, 22, 23) were probably bacillary in origin for the intestines appeared to be the sole seat of the disease. Sydenham's (24) (1669) descriptions of the disease in London and Pringle's (25) reports of the outbreak of dysentery in the army in Flanders (1752) do not mention hepatic complications and are but little different from the records of the dysentery epidemics in recent years which have been proved to have been due to infection with B. dysenteriae. Symptoms, autopsies and, it might be mentioned, even medicinal treatment are practically identical. In the middle ages, epidemics of dysentery were apparently of very frequent occurrence (4).

In England (6, 26) from the beginning of the seventeenth to the middle of the nineteenth century epidemics of bacillary dysentery appeared more or less regularly at twenty-year intervals. It would seem as if the disease would attack each generation, render the survivers immune and then wait for the non-immune offspring.

It would be merely repetition to record the extensive epidemics of dysentery that have been reported. From Iceland to Africa they have been numerous. Epidemics were recorded in North America in the middle of the eighteenth century (27) probably introduced from Europe. Hirsch (4), Kartulis (5), Rogers (3), Gettings (6) and others (7) have completely covered this historical aspect. The importance and efficacy of modern sanitation in times of peace are clearly illustrated by the practical disappearance of extensive epidemics of dysentery from the civilian population. It is not to be denied that the disease is still a menace (28, 29), for it claims many victims especially among

children and the inmates of jails and asylums. In such institutions the high incidence of bacillary dysentery is noteworthy. Baly (30) in 1847 focused attention on its prevalence in English jails and pointed out that not a single liver abscess had been found in Milbank prison among the hundreds of dysentery necropsies from 1823 to 1847 and furthermore that in his experience ipecac which physicians in India had found so efficacious was useless. MacKinnon (31) in 1848 reported a similar condition in the Indian jails. In the insane asylums of England (6, 32) and of the United States bacillary dysentery has proved to be a serious problem. These cases of so-called "asylum dysentery" have now been proved to be due to infection with B. dysenteriae (33, 34, 35, 36, 37, 38). It does not appear (39) to be a seasonal disease whereas the dysentery of barracks and camps is generally much more prevalent in summer and autumn.

Mild, sporadic cases of bacillary dysentery still occur in England (40) and in the United States more frequently than is generally recognized.

Dysentery in children (historical data)

The reduction of the incidence of dysentery in children has not been as marked as in adults (civilians). This may be due to the fact that until the present century it was not recognized that many of the bloody diarrheas of childhood were really cases of dysentery although since 1829 various surmises have been advanced in regard to its infectious or "miasmatic" nature (4). Aretaeus in the second century, Harris in London in 1650 and others (26) mentioned infantile diarrhea and Benjamin Rush (41) in 1777 emphasized the prevalence and serious consequences of bloody diarrhea in infants in the United States. The condition was probably unknown among the American Indians (42). During the nineteenth century the disease was discussed under various names. The medical literature, both American and European, is replete with descriptions of, and observations on, "cholera infantum." This term covered a multitude of sins and not the least of these was bacillary dysentery. The clinical descriptions and autopsies reported by Jackson, Warren (43), and Horner (44) of Boston and others (45, 62) in children with "cholera infantum" and "bloody diarrhea" are similar to those we have had in the past few years

in cases from which B. dysenteriae was isolated. Ekiri (46) was the name given to epidemic infantile diarrhea in Japan and this also is now proved (47, 389) to be bacillary dysentery. At present the disease in children frequently escapes official notice by masquerading under other names of which ileocolitis and "infectious diarrhea" are the more common. Under the blanket term "summer diarrhea" many cases of infantile dysentery are hidden. Although we seldom see epidemics such as were recorded in this country in Revolutionary times, yet many sporadic cases still occur (48).

Dysentery in troops (historical data)

Practically every long campaign and extended siege since the memory of man has produced an epidemic of dysentery. The "emerods" with which the Bible states the army of the Philistines was smitten are now interpreted (350) as prolapses of the rectum occurring in epidemic dysentery. During military campaigns, Edward I and Henry V of England died of this disease. Seventy-five per cent of the latter's army succumbed to dysentery (6). The armies in the Peloponnesian war (4), the British campaigns in the 18th century (49, 50), Napoleon's campaigns, the Crimean war (51), the American Civil war (52), the Franco-Prussian war (6) and the Chino-Japanese war probably paid heavier toll to B. dysenteriae than to Mars. In 1914 Osler (53) said that while typhoid fever would be controlled, dysentery would play havoc. It did. Early in 1915 the hospital ships returned from the Dardanelles (54) laden with cases of dysentery. The Belgians and British in Flanders (55, 56, 383), the British in Salonika (57, 58), Gallipoli (54, 59), Mesopotamia (60, 61, 370), Palestine (63, 380), and Egypt (64), and the French in the Argonne (65) and the East (66) suffered also, while the American army, though later in entering the war, had numerous cases at Chateau Thierry and at the base ports (67, 68). The Germans (69, 70, 71, 72, 73, 433) and the Austrians (74, 75) suffered especially along their Eastern fronts, and even found a new type (Schmitz) (76) of dysentery bacillus among their Roumanian prisoners.

In fact, from the standpoint of the prevention of dysentery in campaigns we are nearly as badly off as Xenophon (2) was during the Greek retreat from Persia.

II. ETIOLOGY

Progress toward the discovery of B. dysenteriae

Emanations from the soil, humidity, altitude, atmospheric changes and other conditions were formerly believed to act as causes of dysentery, and occupation, age, race and previous health as predisposing factors.

Pringle (25) in 1752 after discussing heat and humidity as the remote causes and putrefaction of the blood and scurvy as predisposing factors, concludes with the prophetic statement "But having since perused the curious dissertation of Linnaeus in favor of Kercher's suggestion of contagion by animalculae, it seems reasonable to suspend all hypothesis until that matter is further inquired into."

Lambl (81) in Prague in 1859 made the first step toward unshrouding the mystery by describing amebae in the stools of a child dying of diarrhea. Although he strongly urged the possibility that this might be the real cause of the disease, others (82) were not absolutely convinced of it. Eighteen years later Loesch (83) in Petrograd found numerous amebae both before and after death in dysentery cases. He went one step farther and produced symptoms of dysentery in dogs with this parasite. Kartulis (84) (1883) in Egypt demonstrated amebae in sections of the intestinal walls of all of the 150 dysentery necropsies he studied. This apparently settled the question until Massiocetine (85) in 1889 found amebae in patients without dysenteric symptoms. Grave doubts were then expressed in regard to the pathogenicity of amoebae.

However, after Kartulis (84) in Egypt in 1886 had demonstrated amebae in the liver abscesses of patients who had had dysentery and Osler (86) in 1890 had confirmed the finding, Councilman and Lafleur (87) (1891) settled the pathogenicity of amebae by differentiating amebae coli which occur in normal stools from amebae dysenteriae which produce dysentery. They also remarked that a diphtheritic type of dysentery, which we now know to be bacillary, could be distinguished from amebic dysentery. These researches were soon verified by Schaudinn (88) and the name ameba histolytica was applied to the pathogenic variety.

It now appears that in rare cases, symptoms of dysentery may be due to certain other parasites such as balantidium coli (89, 90), lamblia (91), trichomonas (92, 93), ankylostoma, schistosoma, paragonimus (265), chilomastix mesnili (364) and bilharzia (94), which up to the present have received little attention.

Stool cultures (historical)

During this period of controversy over amebae, many investigators still clung to the belief that some, if not all, cases of dysentery were caused by bacteria. In 1869, ten years after Lambl's discovery, Basch (95) reported the presence of leptothrix filaments in sections of the intestines of patients dying of dysentery. From that date on, various workers described different organisms as the cause of this disease. The earlier investigators believed that many species of organisms (polymicrobic theory) could cause dysentery but Klebs (96) (1887), Chantemesse and Widal (97) (1888) Grigoriew (98) (1892), Ogate (99) (1892) and Celli (100) (1896) each advocated a single variety of bacillus as the etiological agent. Many authorities believe that Chantemesse and Widal described a bacillus similar to that finally reported by Shiga although it was claimed that their organism could produce dysentery in guinea pigs, a phenomenon that cannot be reproduced with B. dysenteriae. Maggiora (101), Arnaud (102) and numerous others (103, 104) claimed that B. coli of exalted virulence produced dysentery. B. pyocyaneus was urged as the cause of dysentery by Calmette (105) (1893) working in Cochin China and also by others (106) in America. The streptococcus was reported as the cause in 1896 by Durham, Mott (32) and others (107, 351). B. proteus has also had many supporters (62, 108). B. fecalis alkaligenes (406, 432), B. enteritidis sporogenes (169) and B. lactis aerogenes (407), are occasionally reported as causes of dysentery.

All of these investigators found these various organisms in the excreta of dysentery patients but no one advanced any real proof that there was a causal relationship between any of these bacteria and the disease dysentery. We know now that the streptococci, B. pyocyaneus, B. proteus and these other organisms, although frequently present in dysentery stools are probably without etiological significance.

In 1898 Shiga (77) conclusively proved that a specific organism which has been named after him was present in the stools of many patients with dysentery and that agglutinins for it were present in the patient's serum. Furthermore, it was not present in normal stools. When injected into rabbits, symptoms of dysentery and toxemia resulted. It soon became apparent that this organism was the cause of the cases of dysentery that Shiga studied.

Two years later Flexner (109) found bacilli which were supposed to be identical with Shiga's organism in cases of dysentery in the Philippines. In the same year Kruse (34) found in Westphalia an organism identical with that of Shiga. In an epidemic of dysentery occurring in a German insane asylum, he also discovered a bacillus that differed in its agglutination reactions from the original Shiga organism. This he called B pseudodysenteriae. Both types were soon demonstrated (33) in cases of dysentery in the United States.

In 1902 Martini and Lentz (110) developed a method for distinguishing the Shiga bacillus from Flexner's bacillus and Kruse's pseudodysentery bacillus by means of agglutination tests and the fermentation of mannite. The former failed to ferment this carbohydrate while the two latter produced acid and no gas.

Park (111) carried out mannite fermentation tests on the organism Flexner had recovered in the Philippines and noted that it produced acid and no gas and therefore was similar to Kruse's B. pseudodysenteriae and not to the Shiga bacillus. It also fermented maltose and saccharose. This is the organism which is now known as the Flexner-Harris bacillus.

In 1902–1903 Strong (112) isolated a mannite fermenting bacillus differing in maltose fermentation from Flexner's organism that also satisfied all of Shiga's postulates for a causative organism. It was found in dysentery stools, it was agglutinated by patients' sera and furthermore when fed to a condemned prisoner it produced dysentery.

In 1903 Hiss and Russell (113) found a mannite fermenting bacillus in the stools of a child with dysentery. This organism, which was christened the Y bacillus, failed to ferment maltose and saccharose and thus differed from the the Flexner-Harris and Strong bacilli. Some authors (133) differ in their reports on the maltose and saccharose reactions of these organisms.

The four organisms, Shiga, Flexner-Harris, Strong and Hiss-Russell-Y have been considered distinct varieties and the most common types The first does not ferment mannite; the last three do, but are separated from each other by differences in the fermentation of maltose and saccharose. The serum of rabbits immunized with the Shiga bacillus will agglutinate practically all strains of dysentery bacilli of similar cultural characteristics. Solimano (373) believes that the biochemical reactions of the Shiga bacillus are its only constant factor and that its agglutination reactions are variable. Cultures of B. dysenteriae (Shiga) it is true are encountered that are or can be rendered inagglutinable (114, 115) but the instances are rare. Ordinary laboratory cultivation usually causes these organisms to become more sensitive to agglutination (431). Serum from animals immunized with the Shiga bacillus will not usually agglutinate any of the mannite fermenting cultures to very high titres.

Monovalent sera made from the three main members of the mannite fermenting group (Flexner-Harris, Strong and Y) although usually agglutinating the homologous strain to higher titres will also often agglutinate the other members of the mannite-fermenting group to partial titre and will sometimes even agglutinate the Shiga bacillus in lower dilutions. In other words, it appears that there are two distinct groups, the non-mannite fermenting bacilli with a single variety, Shiga, and the mannite-fermenting bacilli with three subgroups, Flexner-Harris, Strong and Hiss-Russell-Y.

Etiology of "bloody diarrhea" in children

A great advance in the study of diarrhea in children was made by Duval and Bassett (215) who in 1902 showed that many cases of so-called "summer diarrhea" in infants were due to infection with B. dysenteriae. The Rockefeller Commission (138) in the following summer confirmed the discovery. Similar findings have been reported by other investigators in various parts of the United States, Europe and Japan (40, 47, 48, 124, 149, 150, 151, 152, 153, 154, 389). Tenbroek and Norbury (154) in Boston found dysentery bacilli and agglutinins in the blood of 80 per cent of their patients with bloody diarrhea. My results (48) in a series of patients with bloody stools in Baltimore and Birmingham were identical with those of Tenbroek

and Norbury (154). A clinical analysis of all of these cases of dysenteric infection in children reported by various authors shows that it is practically only from patients who have, or have had, bloody, purulent and mucous stools that B. dysenteriae is isolated. In this country and Japan, bacillary dysentery in children is usually due to infection with B. dysenteriae Flexner. Only 12.5 per cent of my cases (48) and 10 per cent of Mita's cases (389) were of the Shiga variety.

Dysentery bacilli have occasionally been reported in the stools of apparently normal infants (153, 155, 156) and adults (47, 117) who have usually, however, been in contact with patients with dysentery and are probably carriers. They have been isolated from sources having no connection with dysentery patients (157). Many of these cultures are inagglutinable (158) and probably are not true dysentery bacilli. I was unable to find typical dysentery bacilli in the stools of 100 normal children and of 63 children with diarrhea (48) whose stools contained no blood and but little mucus.

Dysentery in children stands out sharply on clinical as well as bacteriological grounds. In fact, in the published studies (138, 154, 48) made in several of the larger cities in the United States, approximately 80 per cent of all of the cases of bloody and mucous diarrhea in children have been proved to be due to infection with B. dysenteriae.

It is thus apparent that ileocolitis and bacillary dysentery in children are one and the same disease. They should be called dysentery. There seems no justification for calling the same disease in children and adults by different names. Nevertheless, many types of diarrhea in children during the warm months, regardless of etiology, are often classed together as "summer diarrhea."

Many bacteriological studies of the stools of children with diarrhea have been made and numerous different organisms have been brought forward as the etiological agents of this condition. The old contention (159) that B. welchii (gas bacillus) was one of the causes of diarrhea in children has been discredited. Numerous investigators (48, 154, 160, 161, 162, 163) have shown that this organism is present in the stools of many normal children and has nothing to do with the etiology of diarrhea.

Several investigators have maintained that B. Morgan No. 1 was the cause of diarrhea in children (164, 165) and also in adults (354).

Numerous investigations (48, 63, 66, 68, 154, 166, 167, 168, 430), have disclosed the fact that this organism is a motile Gram-negative bacillus characterized by the production of acid and gas in the monosaccharides only, the formation of indol and the non-liquefaction of gelatin. It produces an endotoxin fatal for rabbits but no exotoxin (430). B. Morgan probably represents a wide group of bacilli rather than a single type. It is also present in the stools of many normal children and adults. Furthermore the serum of patients with diarrhea in whose stools B. Morgan No. 1 is found, do not have agglutinins for this organism (48, 154, 166) so that it would seem highly improbable that B. Morgan No. 1 is of etiological importance in diarrhea.

The claims that B. pyocyaneus (106), streptococcus fecalis (107), B. proteus (63, 108, 170) and highly virulent colon bacilli are the cause of diarrhea in children have all been frequently refuted (48, 154, 163).

Several investigators (171, 172) have advanced the theory that the diarrheas of children are caused by the effects of a putrefactive or a fermentative flora. The idea has been recently emphasized in the United States (173). Our studies (163) have revealed the fact that the so-called putrefactive and fermentative intestinal flora that have been supposed to produce diarrhea, frequently exist in normal children without causing the slightest change in the patient's health. The putrefaction and fermentation theory of intestinal disease in children is an old one and originated with Jackson (43) of Boston in 1812. "In some cases in which symptoms of dysentery had occurred there was postmortem inflammation of the large intestine which is attributable to the putrefaction of animal food and the acetous fermentation of that which is vegetable." Proof has not yet arisen that gives this theory any more stability than it had in 1812.

The toxins of the Shiga bacillus

Shiga (77) first pointed out that the bacillus which bears his name was highly toxic for rabbits. The Shiga bacillus or its poisonous products induces two kinds of marked lesions in the rabbit (77, 78, 116, 117, 118, 119, 120, 121); one is localized in the intestine, and the other in the central nervous system. Olitsky and Kligler (119) have isolated two toxins from cultures of B. dysenteriae (Shiga) and have dem-

onstrated that they are physically and biologically distinct. The Shiga bacillus grown in egg albumen broth yields in the first few days of the cultivation, at the beginning of the alkaline phase of its growth and before bacterial disintegration sets in, a toxic product which appears in the bacteria-free filtrate. This toxic product is precipitated with the globulin fraction of the protein, is relatively heat labile, being destroyed when heated to 75°C. for one hour, and is capable of inciting antitoxin formation. It is constant in its properties, regardless of the source of the Shiga culture, i.e., an antitoxin produced by the injection of one Shiga culture will neutralize the toxins of other Shiga cultures from widely separated sources. This toxin will produce in rabbits after a definite incubation period, typical lesions of the central nervous system (hemorrhages, necroses, and possibly a perivascular infiltration in the gray matter of the upper spinal cord and medulla) with paralysis of the limbs and urinary bladder (vide infra). It will not produce any obvious intestinal lesions. Olitsky and Kligler (119) regard it as an *exotoxin* and a *neurotoxin*.

The production of the *endotoxin* of Shiga bacilli does not differ essentially from that of other bacteria. The principle underlying all of the methods is that of autolysis or dissolution of the bacterial cell with the resultant liberation of its intracellular components. Most observations with the Shiga bacillus have been made with endotoxins produced in broth cultures by prolonged incubation (beyond fourteen days), but endotoxin may be produced more rapidly by incubating at 37°C. for forty-eight hours a saline suspension of a twenty-four-hour agar slant culture and then filtering through a Berkefeld N candle (119).

Usually small amounts of exotoxin are found in preparations of endotoxin and vice versa but they may be separated by heat for the exotoxin is destroyed when heated to 75°C. for one hour while the endotoxin will withstand this temperature although it is destroyed when heated to 85–90°C. for one hour. These two toxins may also be separated by neutralization, i.e., by adding anti-exotoxin, all of the exotoxin present is combined and neutralized and only the endotoxin remains free and active. Anti-exotoxin will not neutralize endotoxin. Endotoxin, however, is neutralized by an antibacterial serum prepared by actively immunizing horses with Shiga bacilli.

The endotoxin exerts a typical action on the intestinal tract of rabbits producing edema, hemorrhage, necroses, and ulcerations especially in the cecum and large intestine (vide infra). The Shiga endotoxin is probably of intracellular origin, and has the properties of the endotoxins as a class (119). Neitz (122) extracted a nucleo-protein from Shiga bacilli that was toxic for animals. The serum of animals injected with this nucleo-protein would agglutinate the Shiga bacillus.

Horimini (341) has reported that by means of washing and neutralization he has been able to separate the toxins of the Shiga bacillus into four fractions. One attacks the cecum, another the central nervous system, another the small intestine and the fourth produces lesions in the colon.

The mannite fermenting dysentery bacilli, on the other hand, produce endotoxin but usually no exotoxin.

The divisions of the mannite fermenting (Flexner) group of dysentery bacilli

The existence of the Flexner-Harris, Strong and Y types of mannite fermenting dysentery bacilli has been confirmed (36, 80, 123) in various parts of the world and furthermore it has been shown on the basis of the differences in fermentation of other carbohydrates such as sorbite, dextrin, dulcite and rhamnose, that there are probably additional members of the mannite fermenting group of dysentery bacilli (7, 80, 124).

A tremendous impetus was given to the study of bacillary dysentery by the Great War. The publications of the workers of the Medical Research Committee of England, the Royal Army Medical College and others have placed our knowledge of the disease on a new plane. At first there was considerable confusion in regard to the different varieties of mannite-fermenting dysentery bacilli. It had previously been shown that divisions of this group into Flexner-Harris, Strong and Hiss-Russell-Y on the basis of the fermentation of maltose and saccharose were unreliable (35, 37, 56, 57, 110, 130, 222). An organism may be isolated from a patient's stool that gives the fermentation reactions of the Hiss-Russell-Y organism, i.e., not producing acid in maltose and saccharose. If the fermentations are repeated after a

lapse of a few months, they may be identical with those of the Flexner-Harris bacillus, i.e., forming acid in maltose and saccharose. If this organism is then injected into an animal and then recovered and its fermentation ability retested, a reversion to the original Hiss-Russell-Y type may be noted (110). The question then is, what type of bacillus caused this patient's dysentery? Serological results did not always help for many Flexner-Harris and Y monovalent sera will cross-agglutinate to such high titres that it is impossible to decide which is specific. The changing fermentative ability of these divisions probably accounts for the frequent confusion of the sera, for in the example I have just quoted, a diagnostic serum made with the freshly isolated organism, while it gave fermentative reactions similar to a Y bacillus, would of course be called a Y serum. After a few months, however, if a diagnostic serum was made with the same culture which then fermented as a Flexner-Harris bacillus, would this new serum be a Flexner-Harris serum? At any rate, both the original and the new sera will agglutinate this organism that was at one time a Y bacillus and later a Flexner-Harris type, for the agglutinins of the serum do not change their type (222). If a serum reacts with a freshly isolated organism at a dilution of 1/100, it will usually react to the same or a higher titre with this organism after a few months of laboratory cultivation (431). As an exception to this, Benians (114) has just shown that injecting an agglutinable Shiga bacillus suspended in mucilage of tragacanth into a guinea pig may render it inagglutinable. This may, perhaps, be due to the same process involved in Bordet's and Ciuca's (233) experiment (bacteriophage or d'Herelle phenomenon) (vide infra). Cultivation in bouillon containing antidysenteric serum will produce the same result (115, 452). In some instances (378) long cultivation alone may decrease the agglutinability of a strain of dysentery. Werdt and Kopatschek (367) found that all strains of B. dysenteriae when grown on a protein free medium to which test sugars had been added, failed to ferment dextrose, mannite, maltose, lactose or saccharose. Other members of the colon-typhoid group produced their typical sugar reactions. Addition of a small amount of peptone to this protein free medium reëstablished the usual sugar fermentations characteristics of the dysenteries. These investigators conclude from this that dysentery bacilli do not form carbohydrate splitting

enzymes in the absence of protein. It may be seen therefore that in the whole series of dysentery bacilli marked changes may occur or be brought about that will greatly alter both the fermentation capacity and the agglutination characteristics of these organisms. However, although the agglutinability of a dysentery bacillus may occasionally be reduced to zero, yet a distinct change from one serological variety to another does not occur, whereas a change from one fermentative variety to another is quite common within the mannite-fermenting group.

Murray (131) and others (132, 133) have attempted to clarify this question. Murray found that 34 mannite fermenting dysentery bacilli isolated from cases of dysentery in different parts of the world fell into five divisions on the basis of their agglutination reactions with monovalent rabbit sera. These five divisions were designated as the V, W, X, Y, and Z divisions of the Flexner group by a committee of bacteriologists appointed by the British War Office Committee on Dysentery. The names of the various subgroups based on differences in fermentation of maltose and saccharose have been discarded. The name Flexner* is now usually applied to the whole mannite fermenting group and the subdivisions based on agglutination noted, i.e., B. dysenteriae (Flexner, type V, etc.).

I used fermentation tests with maltose, saccharose, dulcite and rhamnose, and also agglutination tests with Murray's five (English) Flexner monovalent rabbit sera types V, W, X, Y and Z to differentiate eighty-nine cultures of mannite fermenting dysentery bacilli isolated from the stools of cases of dysentery in adults and children (132). On the basis of the fermentation tests, these cultures fell into seven groups which did not correspond with the groups obtained by the agglutination tests, i.e. of the organisms that fermented maltose and not saccharose, some were agglutinated by the Y serum and others by the Z serum. Of the organisms agglutinated by the X serum, some fermented maltose and saccharose and others did not ferment saccharose. In order to avoid this confusion either fermentation or agglutination methods must be adopted as the criterion for classification.

*In the remainder of this paper by B. dysenteriae (Flexner) or the Flexner bacillus I shall refer to the whole mannite fermenting group of dysentery bacilli.

Agglutination tests were performed with V, W, X, Y and Z stock cultures and the sera of the patients from whose stools dysentery bacilli were obtained and a general correspondence was found between these serum reactions and the serological grouping of the stool organisms. That is, if the patient's serum agglutinated the V and Y stock cultures, his stool organisms would be agglutinated by the V and Y type sera.

As the fermentation reactions of these cultures may change after subculture and as the serological typing is fairly constant (222), a grouping on the basis of agglutination is preferable. Inasmuch as Murray studied organisms from such widely distributed sources it would seem advisable to adopt his serological classification and to add to it the types that fail to be agglutinated by his V, W, X, Y and Z sera. Polyvalent sera for diagnostic and therapeutic purposes should include antibodies for the more common of these types.

There are probably other types of Flexner bacilli in addition to the V, W, X, Y and Z types (57, 449), for from the stool of one dysentery patient I isolated a mannite fermenting dysentery bacillus that was not agglutinated by any of the five diagnostic sera and there were no agglutinins in this patient's serum for the V, W, X, Y and Z stock cultures (132).

Flexner cultures are rarely agglutinated by only one of these five sera; for example, a strain may react with the Y serum at a high titre and with the W and X sera in lower dilutions. Murray believes that there are five or more antigens in the Flexner group, one of which predominates in a given culture.

Absorption tests and the Michealis "acid agglutination" reaction (57, 134, 135) are of little assistance in the division of the Flexner group.

The toxins of the mannite fermenting (Flexner) group of dysentery bacilli

It has usually been assumed that the Flexner group of dysentery bacilli caused nothing but intestinal lesions because they only produced endotoxin, an enterotoxin, but Thjotta and Sundt (442) have reported that filtrates of eight-day bouillon cultures of one of the subgroups of mannite fermenting dysentery bacilli contained a neuro-

toxin. When these filtrates were injected into animals, nervous lesions occurred after an incubation period, but no intestinal lesions were encountered. These bacilli also possessed an endotoxin which caused intestinal disturbances, usually of a mild character. Repeated injections of the two toxins rendered animals immune. A weak antitoxin could be prepared for each of these toxins.

Geographical distribution of Shiga and Flexner dysentery bacilli

During the war the predominating type of organism varied with the epidemic. On the Gallipoli peninsula (54), along the German and Austrian Eastern fronts (69, 71, 72, 73, 74), in Russia (136), Brittany (137), Albania (90), Macedonia (355), Norway (455), and in the recent British outbreaks (29, 356), the Shiga bacillus was usually more prevalent while the Flexner bacillus was the more common along the Western front in the Allied (69, 55) as well as in the German armies (73), along the Serbian front (70), in Salonika (222), in Brussels (415) and among the civilians in Germany, Austria (69) and South America (387). Two small Shiga epidemics have, however, recently been reported in Germany (357, 368). Flexner and Shiga infections were about equally frequent in Mesopotamia (370). Blackburn (380) states that Flexner infections were more common in Palestine.

In the sporadic cases of dysentery in children the Flexner bacillus is more common than the Shiga variety (48, 124, 138, 139, 140, 389, 418). The statement is sometimes made (140) that mixed Flexner and Shiga infections in children are more common than infection with the Shiga bacillus alone. This has not been true in our series of cases (48). In 35 cases of bacillary dysentery in children in Baltimore and Birmingham, Alabama, I found 31 due to infection with B. dysenteriae Flexner and 4 with B. dysenteriae (Shiga). I did not find any cases of mixed infection.

Intermediate or atypical varieties of dysentery bacilli

In addition to the Shiga bacillus and the various members of the Flexner group, intermediate varieties have been described (141, 389). Three of these types of dysentery bacilli deserve mention. One, a bacillus that forms acid and no gas in lactose, was called B. pseudo-

dysenteriae type E by Kruse (34) and is colloquially known as Kruse E. There is probably a whole group of these bacilli that produce acid and no gas in lactose (39, 142, 143). Andrewes (134) calls the members of this group, B. dispar and doubts their pathological significance. There is no absolute proof that these organisms can cause dysentery but it is not at all unlikely that some of them are pathogens. Hilgers (384) isolated several strains of Kruse E from children suffering with follicular enteritis. He considered it to be identical with Sonne's group III (123). I have recovered Kruse E bacilli (68) that agglutinated with Murray's Kruse E serum in six cases of dysentery in adults and from the intestines of one fatal case of dysentery in a child, and an inagglutinable variety in six additional cases of dysentery in adults and four non-dysenteric cases in children. The sera of several normal individuals agglutinated B. dispar (Kruse E) in dilutions of 1/50.

Schmitz (76) in 1916 during an epidemic of dysentery among Roumanian prisoners isolated a new type of bacillus. This organism is non-motile, produces indol and forms acid and no gas in dextrose and rhamnose. Ornstein (365) working with eight strains of the Schmitz bacillus isolated from dysentery patients has confirmed these results. He also showed it to be distinct from B. fallax. Blumental (377) isolated the Schmitz bacillus in Galicia and considered it agglutinogenically identical with Kruse J bacillus. Andrewes calls this B. ambiguus and is doubtful, as this name implies, of its pathogenicity. Nevertheless it produces dysentery (57). A laboratory technician (144) pipetted a mouthful of culture of the Schmitz bacillus and developed mild dysentery two and a half days later. The Schmitz bacillus was recovered from the stools. Broughton-Alcock (145) recovered this bacillus in two outbreaks of mild dysentery among British troops. Kirschner and Segall found it in cases in Vienna (406). I have recovered it in two cases during an epidemic of dysentery in the A. E. F. (68). No serum that I have tested either from dysentery patients or from normal individuals has agglutinated the Schmitz bacillus in dilutions of 1/20. Somewhat similar organisms have been isolated by other workers (124, 140, 146, 389) and called by various names such as "alkaline" or pseudodysentery bacilli. Flexner believes them to be non-pathogenic (39).

A third organism called B. alkalescens by Andrewes is a mannite fermenting bacillus differing from the Flexner group in that it forms acid (no gas) in dulcite. Three of the four strains that I have encountered in cases of dysentery have not been agglutinated by any of the Flexner type sera. I have not recovered B. alkalescens from normal individuals. The biological characteristics of these various organisms are expressed in table 1.

TABLE 1

Biological characteristics of the various types of dysentery bacilli

TYPE OF BACILLUS	GRAM STAIN	MOTILITY	INDOL	GELATIN	LACTOSE	DEXTROSE	MANNITE	MALTOSE	SACCHAROSE	DULCITE	RHAMNOSE	XYLOSE
B. dysenteriae (Shiga).....	0	0	0	0	0	+	0	Var	0	0	0	0
B. dysenteriae (Flexner)...	0	0	Var	0	0	+	+	Var	Var	0	Var	0
B. dysenteriae (Kruse E) or B. dispar.....	0	0	Var	0	+	+	+	+	+	0	+	+
B. dysenteriae (Schmitz) or B. ambiguus.....	0	0	+	0	0	+	0	0	0	0	+	0
B. alkalescens.....	0	0	+	0	0	+	+	+	0	+	0	−

+ indicates formation of indol, or production of acid and no gas in carbohydrate media.

0 indicates negative gram staining, non-motility, non-indol production, non-liquefaction or non-fermentation of carbohydrate media (twenty-eight-day incubation).

Var (variable) indicates that some members of the group form indol or produce acid and no gas in carbohydrate media while other members fail to do so.

− indicates that a test was not made.

Acid production by dysentery bacilli

Zoller and Clark (416) have shown that under aerobic and anaerobic conditions, in the presence of 1 per cent dextrose, Shiga, Flexner, typhoid and paratyphoid bacilli produce approximately the same total amounts of volatile fatty acids and about the same proportions of formic and acetic acids. When these organisms are grown aerobically on sugar-free peptone water, volatile fatty acids are formed in appreciable amounts. Formic acid, however, is not produced but propionic acid is found in its place. When cultured anaerobically on non-sugar media, these bacteria produce formic acid and also a certain amount of butyric acid. Zoller and Clark suggest that the enormous amounts of formic acid produced by these bacilli may

play a significant part in causing the digestive disturbances and toxic symptoms accompanying their infection of the human gastro-intestinal tract.

Mutation of dysentery bacilli

A certain amount of mutation can be produced in dysentery bacilli. Fletcher (147) has isolated bacilli from the stools of a dysentery carrier and of a convalescent patient that were apparently capsulated and that formed mucoid colonies. Organisms resembling dysentery bacilli (mannite-fermenting) were obtained by plating out peptone water cultures of these mucoid bacilli. These organisms were agglutinated by dysentery serum but did not absorb agglutinins. Maymone (148) reported that Shiga bacilli isolated from the stools of the same patient might differ in agglutinability, absorption and dextrose fermentation.

Arkwright (38) from a single strain of B. dysenteriae (Shiga) as well as from single strains of several different members of the typhocoli group, has obtained two forms. One of these made a stable emulsion in physiological salt solution and the other yielded an emulsion which was spontaneously agglutinated in normal saline (without the addition of serum). These two types were also distinguishable by the difference in their growth. Both of these variants of B. dysenteriae (Shiga) were agglutinated to the same titre by a stock Shiga serum. Sera, made by immunizing animals with each type, however, agglutinated only their homologous strains in high dilutions and showed but very slight cross-agglutination. De Kruif (435) has had somewhat similar results with the organisms of rabbit septicemia.

Twort (348) reported that repeated subcultures of young Shiga cultures eventually showed a preponderance of large thick bacilli. When these were grown anaerobically, and then subcultured aerobically, two types of colonies resulted, A, a large mottled colony composed of waxy long spirochaete like bacilli containing a few granules and B, a gray colony which later became mottled and was formed by long bacilli with swollen ends, some of which appeared to split open and to liberate free granules. When type B colonies were replated, a third type of bacillus was found. These type C organisms were shorter, thick bacilli and they formed waxy colonies. The A, B and

C types gave rise to mixed forms on subculture but they did not revert to their original form. Cultures of the A, B and C types were agglutinated by Shiga serum to higher titres than the original Shiga culture, but spontaneous agglutination was frequent. Type C produced a large amount of acid in maltose, type B formed a fair amount, while type A produced little or none. Twort suggests that these different types represent sexual forms, or that each type has a special function such as toxin production, food production, reproduction, etc. They do not represent a life cycle as they do not revert to their original form.

It is possible that this mutation depends upon the same process that is responsible for the changes in the form of the colonies and in the characteristics of the bacilli that are seen in dysentery cultures which have been acted upon by bacteriolytic filtrates (bacteriophages, d'Herelle phenomen). This will be discussed later.

Relation of length of disease to excretion of dysentery bacilli

It is frequently stated (56, 63, 64) that after the sixth day of the disease in adults it is impossible in the majority of cases to isolate B. dysenteriae even though the stools contain mucus. The percentage of positive stool cultures in typical cases of bacillary dysentery is rarely high (69, 74). Seligman (69, 71) found B. dysenteriae in 38 per cent of all of his acute cases. His highest percentages were in the first few days of the disease (see table 2). Martin and Williams (56) have made an interesting analysis of their 1050 positive stool cultures in cases of dysentery among the Mediterranean Expeditionary Force. Only 15 per cent were positive at the first examination. This emphasizes the necessity for repeated cultures and that single negative examinations are worthless. The earlier in the disease the cultures are made, the higher the percentage of positive results (see table 2), which is somewhat different from the experience with typhoid fever. However, occasional patients excrete the organisms for months (69) and even years (174). Fletcher and MacKinnon (175) have applied the term persistent carriers to individuals harboring dysentery bacilli over three months. Many of them cease to have clinical symptoms of dysentery.

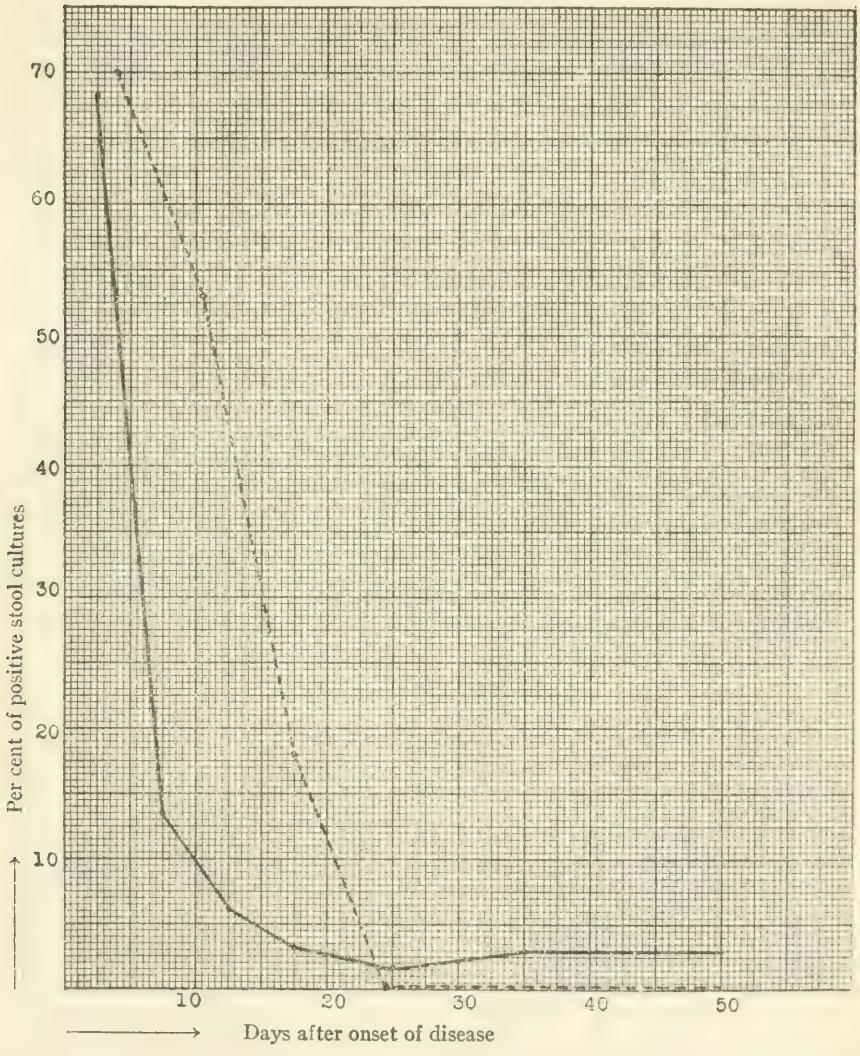

TABLE 2

Graph represents success in recovering dysentery bacilli from the stools at different periods after the onset of the disease. ———— *figures from 1050 cases (Martin and Williams) (56),* - - - - - - *figures of Seligmann (71)*

Collection of stool specimens

For an accurate bacteriological examination the proper collection of stools is of the utmost importance. It is preferable for the bacteriologist himself to collect a specimen of blood and mucus directly from the bed pan or with a rectal swab. When this is impossible, a portion of blood and mucus should be collected on a sterile swab or spatula and sent to the laboratory in a sterile tube or jar as soon as possible. With children, the napkin containing the stool should be placed in a clean container and sent to the laboratory at once. In the majority of cases B. dysenteriae is greatly outnumbered by B. coli and unless the specimens are fresh, the isolation of dysentery bacilli is difficult and often impossible. Friedman (125) suggested that the difficulty in isolating dysentery bacilli from dysenteric stools might possibly be due to the presence of a bacteriophage in the specimen which killed or inhibited the organisms before they could be cultivated. Repeated stool cultures are usually necessary. A negative culture is of no value in the exclusion of the possibility of dysenteric infection. In many mild cases stool cultures are valueless and the *agglutination reactions of the patient's serum should always be performed.*

Viability of dysentery bacilli

Many of the negative results obtained with typical cases of dysentery are due to the age and dried condition of the stool specimens. Dysentery bacilli cannot, as a rule, be cultivated after two days sojourn in feces or eight days in milk unless the mixtures have been kept on ice (34). Pfuhl (176), however, found that the dysentery bacillus remained alive for one hundred and one days in a mixture of feces and moist earth kept at 1° to 5°C. but for only twelve days in dry soil. Schmidt (450) claimed that B. dysenteriae survived all winter in moist soil. Kligler (448) found that Flexner dysentery bacilli survived eight days in feces, seventy days in moist soil and eight days in the fluid from a septic tank when the reaction was between pH 7.4 and 7.8 but only three days at pH 8.6 or over, They could not be cultivated after twenty days in dry soil and ten days in acid soil (pH 5–5.5). I have alternately frozen and thawed a saline suspension of Flexner bacilli once daily for thirty-three days and

found that the organisms remained alive (395). Lauber (368) found that dysentery bacilli soon died out in stools kept at 37°C., becoming overgrown by B. proteus; in the ice box, however, specimens remained positive for B. dysenteriae for as long as ten days. Organisms may survive in dry feces twelve days, in soiled linen nineteen days, in water, in butter, and in cheese nine days (57, 176, 322). I have found that a peptone water culture of Flexner bacilli remained alive after one hundred and fifty two days at 37°C. The bacilli are killed in half an hour by one per cent carbolic acid and immediately by 5 per cent carbolic and 1:2000 solution of corrosive sublimate (39). B. dysenteriae is usually killed by being kept at 0°C. for two months and also by being heated to 60°C. for ten minutes (180, 222). The thermal death point however may vary with different strains. Direct sunlight is said to kill this organism in thirty minutes (222). Stools of dysenteric patients are usually markedly acid in reaction. With increasing acidity of the stool it becomes more and more difficult to find dysentery bacilli by bacteriological methods (371, 382). In Salonika (57) it was found that by mixing equal parts of 3 per cent sodium hydroxide with the specimen the viability of dysentery bacilli was increased so that stool cultures were satisfactory twelve hours after the collection of the specimen.

Technique of stool cultures

A loop full of bloody mucus (unwashed) is streaked over the surface of one Petri plate of Teague's or Endo's medium and then without flaming the loop, it is streaked over another plate. This will usually result in separate discrete colonies on the second plate. I have found Endo's medium (48) satisfactory but now prefer Teague's medium (177,178, 179) of methylene blue eosin lactose agar, as the differentiation of B. coli and B. dysenteriae is more definite. English investigators recommend McConkie's Bile Salt agar (180).

After eighteen hours incubation at 37.5°C. the colorless typhoid-like colonies are fished into tubes of Russell's double sugar medium (178, 180, 181) (Andrade's (182) indicator). Those cultures that have colorless slants and red butts without gas after eighteen hours incubation are subcultured into gelatin and seven Durham fermentation tubes of peptone water containing respectively 1 per cent of lactose, dextrose, mannite, maltose, saccharose, dulcite and rhamnose (brom-cresol purple indicator) (183). The first three carbohydrates are the most essential.

The growth from the original culture (Russell's slant) is then emulsified in saline and agglutinated macroscopically at 55°C. for five hours with polyvalent dysentery, Flexner and Shiga type sera. Six to eight hour peptone water cultures are examined for motility and seven-day peptone water cultures are tested for indol by ether extraction and Ehrlich's reagent (48, 184).

The fermentation cultures are read at intervals for over fourteen days and the gelatin cultures are left at room temperature for twenty-eight days.

The necessity for prolonged incubation of fermentation cultures is shown by the fact that 12 per cent of the cultures from children in our series (48) and 29 per cent of those from the series in adults (68) were late lactose fermenters, that is, formed colorless colonies on Endo's or Teague's medium but fermented lactose after the second day of incubation. All fermentations were practically complete by the 14th day and only very slight changes occurred during the remaining time of the twenty-one day incubation. It would seem that fourteen days incubation for fermentation cultures is sufficient.

Subsequent agglutination work to confirm the original tests or to determine the V, W, X, Y or Z type if the culture ferments mannite is done (macroscopically) with eighteen-hour peptone water cultures.

Agglutination reactions of the patient's serum

Inasmuch as the isolation of dysentery bacilli from the stools requires considerable time as well as training, the agglutination reactions, which are positive after the sixth to the tenth day of the disease, are frequently used in the diagnosis of dysentery. It is often stated that the patient's serum reactions in dysentery are uncertain (46, 70, 185, 186, 187, 222, 356, 385). It is just as commonly claimed that they are of the greatest value (48, 69, 71, 72, 73, 150, 154, 184, 188, 189, 368, 409) and that the serum of normal individuals does not agglutinate B. dysenteriae (190).

The confusion in regard to the reliability of the diagnosis of bacillary dysentery by agglutination is largely due to two things; first that there are five or more types of the Flexner bacillus and if any of these types are omitted in agglutination tests, the sera of some dysentery patients which may agglutinate one of these omitted types, may be reported as negative (48, 57); and second because living cultures are

frequently employed as antigens (191, 222). Living cultures vary from time to time in their agglutinability (114, 115, 192, 193, 194, 195, 431). Therefore agglutination tests made with dysentery cultures killed by formol (standard agglutinable cultures) whose agglutinability does not vary, are much more reliable. It is of the greatest importance that only those dysentery cultures whose sensitiveness to agglutination has been thoroughly tested should be selected for the preparation of "standard agglutinable cultures." Many strains even of the same serological type as the organism producing the patient's disease are not agglutinated by the patient's serum. On the other hand, dysentery cultures are frequently encountered which are agglutinated to comparatively high titres by the sera of normal individuals. Some investigators (196) have, it is true, reported unsatisfactory results with Dreyer's formolized cultures, but the majority find the method extremely useful. Employing the technique outlined below, I have found that agglutinins in a patient's serum in a dilution of 1 to 30 or over, are usually diagnostic of previous or present dysentery infection. In all patients in our series (48) from whom an agglutinable B. dysenteriae was recovered and whose sera were tested, specific agglutinins were found. Very rarely the sera of typhoid patients or of normal children and adults with no history of dysenteric infection will give positive dysentery agglutination reactions. There is evidence to prove that non-specific agglutinins may be present in the sera of typhoid patients (197, 198, 199). Occasionally the serum of patients with dysentery may agglutinate B. paratyphosus B (379).

Agglutinins for B. dysenteriae are usually demonstrable after the sixth day of the disease, although they are occasionally reported earlier (38, 200). The serum of one child was positive on the second day (48), the titre rising on the fourth (198) and ninth days. The maximum titre is probably reached on the seventeenth to twenty-first day as it is in typhoid fever (57). The titre of a dysentery patient's serum for dysentery bacilli is practically always lower than that of a typhoid patient's serum for typhoid bacilli, probably because dysentery bacilli are usually less agglutinable than typhoid bacilli. A dilution of 1 to 250 especially in Shiga infections is the usual limit at the height of the disease (seventeenth to twenty-first day) but in a few cases of

Flexner infection I have found agglutination for the Flexner bacillus as high as 1 to 1000. However, these titres depend upon the agglutinability of the cultures used in the test. Agglutinins may persist longer than four months. In the sera of four children tested after six months they were still present (48, 57, 69). Agglutination for both Shiga and Flexner groups is occasionally found in single infections with either one of these bacilli (55, 57, 69, 201). I found this in two of our cases (48). True double infections with both Flexner and Shiga types have, of course, been reported (57, 69, 138, 140, 202).

Agglutination technique

I have obtained consistent results with Dreyer's technique (48, 194, 203) but inasmuch as I have used eleven different antigens I have adopted the following modification of this method for all routine agglutination tests in diarrhoeal diseases:

One cubic centimeter of the patient's serum is diluted ten times. 0.5 cc. (or 10 drops) of this diluted serum is placed in each of 11 agglutination tubes, 0.5 cc. (or 10 drops) of a formolized standard agglutinable culture of each of the following organisms is each placed in one of these 11 tubes: B. typhosus, B. paratyphosus A, B. paratyphosus B, B. shigae, B. dysenteriae (Flexner), English types V, W, X, Y, and Z, B. dysenteriae (Kruse E) or (B. dispar) and B. dysenteriae (Schmitz) (or B. ambiguus). In localities where other types of pathogenic intestinal organisms, such as atypical paratyphoid bacilli (69, 204, 205, 206, 207) (Salonika, Bagdad and India) or B. Gaertner (208) are common, they should be added to the series.

These tubes are incubated in a water bath at 55°C. for four and one-half hours. If agglutination is positive for any of these 11 antigens at this 1 to 20 dilution, tests are set up according to Dreyer's directions, using only those standard agglutinable cultures for which there have been agglutinins in the preliminary test.

Blood cultures

Blood cultures, as a general rule, are of but little assistance in cases of dysentery for only in rare instances do dysentery bacilli enter the blood stream. Tenbroek (209), Schloss (210) and others (188, 211, 212, 218) have reported occasional positive antemortem blood cultures for B. dysenteriae. Caussade and Marbais (213) found the Shiga bacillus in the blood stream of one patient although stool cultures were negative.

Dysentery bacilli have been found in a few instances (37, 57, 140, 188, 214, 215) in the heart's blood, mesenteric glands and spleen at autopsy but such findings are the exception (138). Recently positive blood cultures of B. fecalis alkaligenes (216) have been reported in a few cases of bloody diarrhea in children, as well as in an adult with a typhoid like disease (432).

Urine cultures

In one child with bacillary dysentery we found (217) typical B. dysenteriae (Flexner) in the catheterized urine. Fraenkel (218) cultured the urine of 39 patients with mild bacillary dysentery and found B. dysenteriae (Flexner) in three. In the urine of another patient B. dysenteriae and B. typhosus were associated. Sonne (123) reported the presence of Flexner bacilli in the urine of a typhoid convalescent and others have occasionally found bacilli morphologically and culturally indistinguishable from B. dysenteriae in the urine of patients with pyelocystitis (219) and other diseases (218, 220) but proof that all of these urinary organisms were true dysentery bacilli was not brought forward.

The infrequence of positive cultures of B. dysenteriae in the blood and urine renders the taking of blood and urine cultures of little or no diagnostic assistance.

Bacteriological diagnosis (summary)

The highest percentage of positive cultures of dysentery bacilli is obtained from culturing the postmortem scrapings of the mucous membranes of the ulcerated intestines of patients, both adults and children, dying of dysentery. Frequently over 80 per cent of these cultures are positive. The next highest percentage is obtained by culturing the bloody mucus of the feces of children with dysentery; from 50 to 60 per cent of these cultures are positive if cultures are made from several specimens during the height of the disease (from the fourth to fourteenth day). It has been reported (221, 405, 406) that the diagnosis of dysentery is rendered easier by the examination of the rectal mucosa and by obtaining cultures directly from the intestinal ulcers of adults, infants and young children by means of a

proctoscope. However, perforation of the intestine and death from peritonitis has occurred from the use of a sigmoidoscope (446). The lowest percentage of positive stool cultures is obtained in adults (56, 69, 71); 25 to 40 per cent of the cultures of the feces of adults with dysentery may be positive if cultures are repeated during the height of the disease (up to the fourth week).

These percentages of positive cultures of dysentery bacilli are usually only obtained under ideal conditions, i.e., fresh fecal specimens that have not been allowed to become dry and an experienced bacteriologist with good media. Frequently the percentage of positive stool cultures is not sufficiently high to be of great assistance in clinical diagnoses, for even repeatedly negative stool cultures do not rule out the presence of dysentery. Moreover, two to three days are usually required for stool cultures. However, after the sixth to the tenth day of the disease a method is available that is more rapid and that is positive in practically all cases of dysentery and negative in practically all non-dysenteric cases. The agglutination reactions of the patient's serum fulfill all of these conditions after the sixth to the tenth day of the disease in adults and are frequently positive in low dilutions on the fourth day of the disease in children. As I have pointed out, this method is reliable with standardized technique and should be used as an aid to the diagnosis of all diarrheal disease. If the agglutination reaction of the patient's serum is positive for any of the dysentery bacilli, a diagnosis of past or present dysentery (or of prophylactic vaccination) can be made. The exceptions to this are infrequent. If the agglutination reaction is repeated quantitatively after an interval of four days and a marked increase or decrease in the titre of the serum is present, a diagnosis of active dysentery can be made as the titre of the serum of patients who have had dysentery some time previously or who have received prophylactic inoculations of vaccine soon reaches a constant level and tests made at short intervals will show no change. If the agglutination reaction of the patient's serum is negative for all of the dysentery bacilli, the disease can usually be ruled out but the test should be repeated two or three days later.

For a bacteriological diagnosis before the sixth day of the disease stool cultures are necessary. If negative, they should be repeated.

III. FILTERABLE "SUBSTANCE" ANTAGONISTIC TO THE DYSENTERY BACILLUS (D'HERELLE'S PHENOMENON, BACTERIOPHAGE, BACTERIOLYTIC AGENT, BACTERIOLYSANT, ETC.)

Under these names, which have been used interchangeably, an extensive literature has accumulated in regard to a "substance" contained in filtrates of stool cultures and also obtained from other sources which when added to young cultures kills and dissolves dysentery bacilli and other organisms. It has usually been assumed that Twort (126) was the first to describe this phenomenon though Hankin (426) in 1896 demonstrated that the water of the Ganges and Jumna rivers in India was bactericidal for bacteria in general and for the cholera vibrio in particular. Inasmuch as heating the water to 115°C. for a half hour (a temperature which destroys bacteriophagic activity) did not totally destroy its bactericidal activity, Hankin was probably not dealing with a bacteriophage. Nicolle (425) in 1907 reported that cultures or filtrates of B. subtilis would dissolve pneumococci, staphylococci, B. typhosus, B. coli, V. cholerae and B. shigae. Though not recognized as such, this is perhaps the first mention of "bacteriophagy."

Source

There have been at least five methods described by which a bacteriophage may be obtained.

1. Twort (126) in 1915 noted in a culture of staphylococci obtained while plating out glycerinated calf vaccine, transparent areas in which no cocci grew or if they had grown, they had become degenerated. If one of these transparent areas was touched with a sterile platinum loop and the loop was then drawn (without flaming) across the surface of a twenty-four hour agar culture of staphylococci, a streak marking the track of the loop became clear and transparent within a few hours. He then passed the material from these transparent areas through a Berkfeld filter and found that it would dissolve and kill most of the organisms in fresh staphylococcus agar cultures even when diluted one to a million. This bacteriolytic property could be passed on to numerous generations by adding a filtrate to successive fresh staphylococcus cultures and then refiltering. Gratia (376) has recently confirmed Twort's work.

2. D'Herelle (125) in 1917 inoculated two to three drops (or a piece the size of a pea) of a stool from a convalescent dysentery patient in 20 cc. of broth and filtered this culture through a Chamberland No. 12 filter. A trace of this filtrate would dissolve and kill broth or agar cultures of B. shigae. A loopful of the filtrate obtained by filtering this dissolved culture through a Chamberland filter would again dissolve a fresh culture of B. shigae. By similar methods bacteriolytic filtrates active against various strains of organisms have been obtained from the urine of a convalescent dysentery patient (125), from the urine of patients with pyelonephritis (125), from the stools of patients suffering from dysentery (125, 391, 392, 395, 397), typhoid and paratyphoid fever (125, 392, 394), gastric carcinoma (392), rheumatic fever (392), pthisis (392), peritonitis (392, 397), and diarrhea (126, 395), from the stools of cases of avian typhoid in chickens (125), of hemorrhagic septicemia in cattle (125), of plague in rats (125), of flacherie in silk worms (125), of distemper in dogs (126) from the blood of white rats fed on typhi murium (125), in Paris city water (391), in water from the Seine (391), in earth (391) as well as from the stools of normal adults (125, 391), children (395) and animals (125, 391).

3. Bordet and Ciuca (233) injected a culture of B. coli intraperitoneally into a guinea pig. The day after the third injection they found that a small quantity of the resulting peritoneal exudate as well as the culture of B. coli isolated from this exudate would dissolve an eighteen-hour culture of the strain of B. coli that had been used for these inoculations. This lysis was not complete and a few colonies could be cultivated. If these surviving organisms were inoculated into another eighteen hour colon culture, lysis would again result. This bacteriolytic action could in this way be repeated indefinitely. The bacilli exposed to the lytic substance acquired the ability to transfer the lytic property to subsequent generations. Wollstein (397) repeated this work using a strain of the Shiga bacillus instead of B. coli and obtained a bacteriophage active against dysentery and other bacilli.

4. Kuttner (394) found that a filtered glycerine extract of the small intestine of a guinea pig and a saline extract of a guinea pig's liver were bacteriolytic for typhoid bacilli. This lytic principle could be trans-

mitted by passage through successive typhoid cultures. Glycerine extracts of the large intestine and of muscle tissue were not bacteriolytic.

5. I found that if one to sixty day old broth or peptone water cultures of recently isolated or old laboratory strains of B. dysenteriae (Shiga) or (Flexner) were filtered (395), the filtrate in many instances was slightly bacteriolytic against Shiga and Flexner bacilli. Bacteriolytic substances have been reported by others in cultures of B. dysenteriae (126, 397, 438) and D. mucoides (423).

Non-specificity of bacteriolysants

Originally it was thought that the lytic action of a filtrate was specific (125, 126, 233) and that only the organism producing it or causing the patient's infection would be attacked. Later it was reported (125, 429, 376) that no two bacteriophages were alike, some were active against several species of bacteria, others only against one. At present it is believed that all bacteriophages can be made practically omniverous by adding them to cultures of other bacilli, incubating and then filtering the preparation. This may have to be repeated several times before the filtrates will lyse the organism with which it is being cultivated. In this way "bacteriophagy" has been extended to several stains of the following groups, Shiga, Flexner, typhoid, paratyphoid A and B, colon, proteus, hog cholera, etc. (125, 233, 376, 395, 397). Other organisms such as Friedlander's bacillus, B. avisepticus, B. Morgan, etc. have been tested with negative results (397).

Variations in the titre of bacteriophagic activity

Some filtrates may cause lysis when diluted over a million times while others are only active after passage through several successive cultures. The potency of the lytic principle of subsequent generations of filtrates may vary, however, in some being greater than that of the original filtrate (125) in others less (395) and in others the same (394). The lytic power of filtrates which have become contaminated by air or stool bacilli and have been refiltered are sometimes greater and sometimes less than that of the original uncontaminated filtrate (395). Filtrates obtained from the stools of a dysentery patient were some-

times more and sometimes less active against the dysentery bacillus isolated from that patient than against other strains. The bacteriolytic power of a filtrate may vary for different subcultures of the same strain, for cultures isolated from the same patient at different stages of the same disease (125, 395) as well as for subcultures of different colonies fished from the same stool culture (395). The greater the concentration of the bacteriophage, the more rapid and complete is the bacteriolysis (125, 395), i.e., a filtrate which dissolved a culture in three hours when diluted 1:10 usually required 12 hours when diluted 1:100 (394). There are evidently two steps in the d'Herelle phenomenon, first, the organisms are killed and second, they are dissolved. If there were more than 500 million bacteria per cc. only the first step occurred (125). This may possibly be due to the fact that the bacteriolytic principle is adsorbed by the more concentrated bacteria. I found (395) that broth cultures of Flexner bacilli which contained 100 million bacilli or more per cubic centimeter at the commencement of the experiment contained less than 30 viable organisms per cubic centimeter after twenty-four hours contact with an anti-Flexner bacteriolysant. The number of bacteria killed was usually proportionate to the amount of bacteriolysis. There is evidently an optimum concentration of bacteria for if the numbers present were very small, they were destroyed more slowly than when in large numbers (438).

Factors influencing bacteriophagic activity

Temperature. The lytic power of a filtrate is destroyed by being heated to 75°C. for a half hour (127, 394). It is still active after one hour at less than 0°C., four years at 37°C. (127), one hour at 64°C to 65°C., or a half hour at 70°C. (127, 394), though its power may occasionally be diminished by these two latter temperatures (395). The rate of lysis was twice as rapid in a culture and bacteriophage incubated at 41° to 42°C. than at 37°C. (394): at 15° to 16°C. it proceeded very slowly (125) and did not occur at all when the incubation temperature was from 45° to 50°C. (394).

Reaction and oxygen supply of the media. Gratia (376) showed that the inhibition by the lytic agent on the growth of B. coli was slight at pH 6.8, 7.0 and 7.4 but much more pronounced at pH 8.0 and 8.5. Lysis was more complete at pH 8 and 8.2 than at pH 6 to 7.7 (395).

A bacteriophage was active in media with reactions from pH 2.5 to 8.4 but lost its power when the hydrogen ion concentration was above pH 2.5 and below 8.4 (424). Wollstein (397) reported that the lytic action proceeded as rapidly and as completely in the absence of oxygen as in its presence.

Chemicals. A substance having bacteriolytic power has been precipitated from filtrates by the addition of acetone (127), alcohol (127) ammonium sulphate and tricalcium phosphate (439). Kabeshima (127) reported that the lytic agent was soluble in ether and that the addition of 1 per cent sodium fluoride would not destroy the lytic power of a filtrate but both statements have been denied (125, 128). Bablet (128) claimed that glycerine and chloroform inhibited lytic activity. Eliava and Pozerski stated that twenty-four hours' contact with 2.5 per cent phenol or 2.5 per cent sodium fluoride did not affect a bacteriophage but that 0.75 per cent quinine chlorhydrate reduced the lytic activity of a filtrate and that 1.0 per cent destroyed it. De Poorter and Maisin (439) reported that the lytic agent was destroyed by phenol and certain metallic salts and that it was insoluble in animal and plant fats and lipoids. Lytic activity was destroyed by the addition of N/5 sodium hydroxide (395). Four per cent collodium membranes were impermeable to bacteriophages (422).

Other factors. Young living cultures are essential for the action of a bacteriophage (125). Two to eight hour cultures are the most sensitive (394, 395, 397). Dead cultures are unaffected (125, 395). Although young organisms suspended in bouillon peptone water or serum are lysed, saline suspensions are not affected (233, 391,392, 394) unless the reaction is near the optimum (395). A bacteriolytic filtrate loses its power after three or four passages in sterile broth (125, 126, 392) or peptone water (395).

Separation of cultures into "resistant" and "sensitive" types by the action of bacteriophages

When a lytic strain of organisms or a culture that had been attacked by a bacteriophage was plated on agar, two types of colonies appeared (125, 233, 376, 394, 395, 397, 424, 428). These two types were also noted in a culture of a stool of an infant with dysentery (397), as well as in platings of peptone water cultures of normal Flexner bacilli

(395). One was regular and round, resembling a typical colony of the organism. Subcultures of these always gave rise to round colonies. They were not readily dissolved by the lytic agent and were designated the "R" or resistant type. The other colonies were irregular in outline and had a "moth eaten" appearance. They were readily lysed by the lytic culture and were spoken of as the "S" or sensitive type. Subcultures of these gave rise to both regular and irregular colonies.

The resistant strains of Shiga bacilli were composed of regular, equally sized and evenly staining bacilli with some larger forms but few if any coccoid or swollen round forms. Threads were seen in older cultures of the "R" type (397). They grew slowly (376). Broth cultures were not uniformly cloudy and the bacilli rapidly sedimented to the bottom of the tube (424). Resistant organisms were practically inagglutinable and very virulent (125, 233, 276, 397). The "R" type of B. coli was extremely motile, decolorized neutral red and was only slightly phagocytable (376). D'Herelle (125) stated that resistant forms might become coccoid and acquire capsules. Resistant forms may lose their resistance after subculture (125, 428).

The sensitive strains of Shiga bacilli were composed of short bacilli and many coccoid and round swollen forms (397). The "S" type of B. coli grew rapidly in artificial media, was non-motile and did not decolorize neutral red (376). The filtrates of sensitive cultures usually had bacteriolytic power (395, 397) while only a few of those of resistant organisms were active (428). These lysogenic resistant strains might afterwards lose their lysogenic power (428). Sensitive bacilli might gradually die out after repeated subcultures (397) though Bordet and Cuica (233) found that lysogenic colon bacilli retained their lytic power even after 150 transfers.

Gratia (376) isolated eleven types from the original Bordet strain of B. coli that differed in resistance, motility, mucoid growth, ability to yield mucoid growth, fluorescence and sero-agglutination. All of these types produced indol and fermented carbohyrates except saccharose.

There is a striking similarity between the various types of organisms that may be obtained from a culture as a result of the action of a bacteriophage and those that have been described as occurring spon-

taneously or as the result of changes in environment (vide supra, Mutation of dysentery bacilli). Inasmuch as strains closely resembling resistant and sensitive types may be obtained in platings of aged cultures (376, 395) and in cultures of B. coli of different motilities (376), it is probable that this separation of a culture into various types is a result of several independent factors rather than of the action of a bacteriophage.

Results of inoculation of bacteriophages in animals

The injections of bacteriolytic filtrates into rabbits (125, 127, 233, 395, 428, 429) and into the larvae of the beeswax moth (129) have demonstrated that bacteriophages were non-pathogenic and that animals and larvae became immunized to the organisms against which the bacteriophage was active (125, 127, 233, 395). After injection into an animal, the bacteriophage persisted in the intestine for several days (454). The rabbit sera would agglutinate these organisms (395, 397) and were also antilytic, i.e. would precipitate a lytic filtrate (233, 395, 453) and when added to a bacterial suspension and a bacteriophage (even bacteriophages other than the one used in the production of the antilytic serum (429)) would prevent lysis for at least forty-eight hours (125, 233, 438). The sera of animals immunized with lysogenic cultures were also antilytic, though sera produced by the injection of normal organisms had little (438) or no such power (233). Treatment of lysogenic colon cultures (233) and of resistant forms (428) with antilytic sera caused the former to become resistant and to lose their lytic power and the latter to lose their resistance. However, the colon bacilli that had lost their lytic activity became lysogenic again after twenty-one transfers on culture media (233). An antilytic serum apparently had an "anti-immunizing" effect for a mouse injected with one-tenth of a lethal dose of Shiga toxin plus 0.2 cc. of an antilytic serum died in thirty hours. Control mice inoculated with full lethal doses died in four days (125).

It would seem possible that the properties acquired by the sera of these inoculated animals are not due to the antigenic effect of the bacteriophage per se but are a response to the injection of the proteins of the dissolved bacteria although this has been denied (422). The anti-lytic power of the serum is probably a response to the injection

of the bacteriolytic ferment which the filtrate contains and is perhaps comparable to the anti-tryptic power of serum of animals inoculated with trypsin. The immunization of rabbits with anti-Shiga bacteriophages (125, 127) is perhaps due to the formation of dysentery antitoxin, for a bacteriophage obtained by the lysis of Shiga bacilli contains Shiga toxin for several days (127).

Bacteriolysants as therapeutic agents

It was obvious to many observers (125, 395, 397) that this filterable "substance," which would kill and dissolve dysentery and other organisms in vitro, was non-pathogenic and would immunize animals, should be tried therapeutically. D'Herelle (125) reported that in seven cases of severe dysentery in children, three and one-half to twelve years of age the ingestion of 2 cc. of an anti-dysenteric bacteriophage was followed in from twenty-four to thirty-six hours by the disappearance of blood and bacilli from the stools. Friedmann (125) was unable to confirm this. D'Herelle also reported striking therapeutic and prophylactic benefit from the ingestion and injection of 0.25 cc. to 1 cc. of appropriate bacteriophages in epidemics of avian typhoid in chickens, plague in rats and hemorrhagic septicemia in cattle. He stated that the intravenous injection of 500 cc. of blood from one of these inoculated cattle would protect another animal from a lethal dose of living organisms. It is difficult to reconcile this result with his earlier work on the "anti-immunizing" effect of the serum of a rabbit inoculated with an anti-Shiga bacteriophage.

I have treated twelve children two months to four years of age suffering from Flexner dysentery with bacteriolysants which were tested and found to be active against the organisms causing the patients' infections (395). In this small series, even though I administered amount of 5 to 1381 cc. by rectum, by mouth or by nasal tube into the stomach, I was unable to observe the slightest benefit or harm from bacteriophagic therapy. It would seem probable that these large amounts in young children would be as beneficial as the ingestion of 2 cc. which d'Herelle found so efficacious in older children. Larger series alone will demonstrate the practical value of bacteriolysants.

As a matter of fact although it has been frequently proven to be harmless in animals with various infections it is theoretically difficult to explain why the administration of an anti-dysentery bacteriophage to dysentery patients is not harmful. The intestinal lesions of dysentery are due to endotoxin (119) and it would seem probable that if the dysentery bacilli in the intestinal tract were lysed as a result of the administration of a bacteriophage, a large amount of endotoxin would be liberated.

Theories in regard to the nature of bacteriophages

There are at least five hypotheses advanced to explain the nature and mode of action of bacteriophages;

1. D'Herelle (125), inasmuch as he was able to preserve his bacteriophages for over a thousand successive transfers from one Shiga culture to another with no diminution of the strength of the lytic agent (in fact the lytic power increased) believed it must be a living culture and not a ferment. This culture he called the "microbe filtrant bacteriophage" or "bacteriophagum intestinale." He reported that the clear bare areas, which were noted when a bacterial suspension to which a bacteriophage had been added, was plated out on agar, were proportional to the amount of bacteriolytic filtrate added to the preparation and not to the number of bacilli in the suspension, and that therefore these areas represented colonies of the bacteriophage and did not result from the lysis of sensitive organisms as others (233, 376, 394) have maintained. D'Herelle (125) summarized his views as follows:

The bacteriophage is an ultra microscopic organism, which is very widely disseminated in nature. It only multiplies in contact with living bacteria. It penetrates into the interior of an organism and forms a colony of 15 to 25 elements in the space of an hour and a half. The organism then bursts, liberating the young ultramicrobes. These utilize for their development the bacteria which they dissolve with the aid of the lytic diastase which they secrete. There is only one species of bacteriophage and this can acquire activity against any organism. Bacteria on the other hand can also acquire resistance to the bacteriophage. Infection and death or immunity and recovery depend upon whether the organism or the bacteriophage triumphs in this battle. The products of the bacteria which have

been dissolved by the bacteriophage also play an active rôle in stimulating the formation of antibodies. The outcome of an epidemic also depends upon these two forces for the active bacteriophage, the agent of immunity, as well as the bacteria causing the epidemic can spread from one individual to another.

D'Herelle (125) suggested that wholesale protection of the population might be accomplished by introducing a quantity of the bacteriophage into the central supply of drinking water.

2. Kabeshima (127) suggested that the phenomenon depended upon the interaction of a catalyst and a proferment, the former being derived from the host while the latter was present in or produced by the bacterium. He believed that this catalyst was produced by some intestinal gland or by the intestinal leukocytes of dysenteric or typhoid patients as a result of an invasion of pathogenic bacteria, i.e., as a protective measure against infection. This catalyst caused bacteria to produce autolytic ferments. These ferments then acted as catalysts to other bacteria and so on from generation to generation. The fact that this substance would withstand being heated to 70°C., that a very minute quantity of filtrate would dissolve a large number of bacilli in a few hours, that it could be kept at 37°C. for four years without undergoing deterioration, that the bacteriolytic substance was not affected by chemicals which destroy most forms of bacteria, suggested that the lytic principle was a ferment and not a living organism (127). D'Herelle (125), however, protested that spore-bearing and other bacteria could satisfy all of the chemical and thermal conditions which Kabeshima had advanced against the hypothesis that a bacteriophage was a living microbe.

3. Bordet and Ciuca (233) suggested that the ability to produce the lytic substances was acquired by bacteria as a result of contact with some external stimulus such as the leukocytic exudate of the peritoneum of a guinea pig. This external influence possibly represented a defense mechanism on the part of the animal. These bacteria were then able to transmit to their descendants the apitude to form this lytic substance or this apitutude for autolysis.

4. Salimbeni (393) suggested that the d'Herelle phenomenon was probably due to some stage in the history of a pleomorphic organism. He examined in a van Tieghan chamber the changes induced

in a culture of B. shigae by a bacteriophage. He found in addition to the dysentery bacilli a number of small, round or slightly elongated bodies. These developed into typical myxamoebae which ingested and digested the Shiga bacilli. He suggested the name Myxomyces shigophagus for this myxamoeba. Dumas (391), Pettit (393) and Wollman (422) have reported the presence of myxamoebae in their preparations but d'Herelle (125) could find none in his. Whether all instances of bacteriophagy are due to Myxomyces shigophagus or whether these observers were dealing with preparations contaminated by myxamoebae awaits further study.

5. Kuttner (394) proceeded on the theory that the so-called phenomenon of d'Herelle might be due either to an activation of the natural autolysin present in all bacteria, or to the removal of an autolysin inhibiting substance. Once this natural autolysis was liberated, it could in turn liberate an active autolysin from the next generation of bacteria and so on indefinitely. The fact that the autolysin of old or dead cultures cannot be thus reactivated would seem to invalidate this theory.

Discussion

Although much of the evidence is contradictory and unconfirmed, so that it is impossible to form a definite conclusion in regard to the nature of this lytic agent, yet at present the most probable hypothesis is that the lytic agent is an enzyme. The majority of the data with the marked exception of Salimbeni's (393) observation can best be explained on the basis that the lytic principle is an enzyme. Temperature, chemicals, the reaction of the media and the concentration of bacteriophage and bacteria all have an influence on bacteriophagic processes which is similar to that which they have been demonstrated to have on enzymatic phenomena. The optimum reaction for bacteriophagy corresponds very closely to that of the enzyme trypsin. The fact that cultures of lytic organisms as well as bacteriolytic filtrates will not liquify gelatin, however, suggests that the bacteriolytic principle is not trypsin (395). The addition of trypsin to a dysentery culture will not cause the culture to become lytic. It is possible that the bacteriolytic enzyme may be similar to erepsin for the extracts of intestine and liver that Kuttner (394) found to be lytic probably contained erepsin.

It is probable that this bacteriolytic enzyme is both extracellular and intracellular. If the growth of irregular sensitive colonies on an agar plate is suspended in saline and the suspension centrifuged at high speed and the supernatant fluid passed through a Mandler filter, the filtrate is lytic. If the sediment of organisms is resuspended in saline and this suspension ground in a rotary agate mortar and then filtered, this filtrate is equally lytic (395). The fact that living bacteria are necessary for the transmission of the lytic agent suggests that the lytic agent is not the result of the disintegration of dying or dead cells, but represents either the metabolic excreta of bacteria or the synthetic product of the medium elaborated by the action of the bacteria.

If it is granted that the bacteriophagic principle is enzymatic there are at least two possibilities as to its origin. First, as a result of the stimulus of intestinal secretions, tissue extracts, leukocytes, etc., the bacteria acquire the ability to produce bacteriolytic enzymes and this property becomes an hereditary one. This hypothesis requires the assumption that entirely new characteristics can arise as the result of an external stimulus and though perhaps possible is not probable. Second, certain of the bacteria in any culture already have this ability to produce bacteriolytic eryzmes even though it is only slightly developed and that as a result of the action of intestinal secretions, tissue extracts, leukocytes etc. the multiplication of these lytic or sensitive organisms is favored. Such an hypothesis would also explain the facts that filtrates of normal stock cultures were slightly lytic and that irregular colonies were occasionally found in subcultures of normal strains. Bail's (438) demonstration that broth in which normal Shiga bacilli were repeatedly grown and then centrifuged out, was bacteriophagic strengthens this hypothesis. The small amount of lytic substance produced by each growth of organisms remained in the broth and after several reinoculations it became sufficiently concentrated to be readily demonstrable.

Furthermore the explanation is comparable to other bacteriologic phenomena. For instance Teague and Morishima (440) demonstrated that cultures of so-called non-xylose fermenting typhoid bacilli contained a certain number of organisms which fermented xylose slowly and that by suitable cultivation, rapidly fermenting subcultures

could be obtained. Another comparable example is furnished by the increase in virulence of cultures which is produced by animal passage. Growth within the animal probably favors the multiplication of virulent organisms of the culture at the expense of the non-virulent. Gratia (376) has demonstrated that 11 different types could be isolated from the original Bordet strain of B. coli, so that the second hypothesis appears plausible.

The nature of the external influence contained in intestinal secretions, tissue extracts, leukocytes, etc., which favors the development of organisms is unknown. The one factor that is common to all of these stimuli is that they apparently contain a bacteriolytic enzyme similar to, if not identical with that of the lytic organisms.

It would seem that inasmuch as bacteriolytic filtrates may be obtained from so many sources having no relation to the type of organism attacked by the lytic principle that d'Herelle's phenomenon is not an immunological reaction. The fact that Gengou (427) demonstrated that an extract of the leukocytes of normal animals was non-specifically bacteriolytic would seem to invalidate the suggestion of Bordet and Ciuca (233) that the bacteriolytic power of the peritoneal exudate of guinea pigs inoculated with B. coli was evidence of a protective mechanism against bacterial invasion.

Conclusion

According to the data available at present, d'Herelle's phenomenon probably depends upon a bacteriolytic enzyme produced by bacteria. The amount of this enzyme produced by a culture can be increased by external influences such as intestinal secretions, tissue extracts, leukocytes, etc. The action of these external influences is probably to favor the development of lysogenic organisms at the expense of the non-lysogenic. This enzyme not only dissolves organisms but also favors the multiplication of bacteria which produce this enzyme. In this way the bacteriolytic principle is carried from generation to generation. It is highly improbable that this phenomenon represents a defense mechanism on the part of an animal against bacterial invasion.

IV. EXPERIMENTAL DYSENTERY

Virchow (223) and Rokitansky (224) before the discovery of B. dysenteriae and its toxins attempted to explain the localization of the lesions of dysentery. The tendency of the membranous lesions of the intestine to confine themselves to the caecum and colon led Virchow (223) to assume that these lesions resulted from the action of products of decomposition upon the intestinal mucosa which was *already* the seat of catarrhal inflammation, and that the projecting points, the cecum, rectum and flexures of the colon were the most affected because the faeces remained in contact with these parts the longest. It is still believed by many clinicians that dysentery, especially in children, is preceded by a non-specific intestinal catarrh. Rokitansky (224) compared the action of dysentery to that of caustic acids and suggested that the necrosis was due to a direct chemical change in the tissues caused by an action starting from the surface. Zoller and Clark (416) suggested that the enormous amounts of formic acid produced by Shiga and Flexner dysentery bacilli might play a significant part in causing the digestive disturbances and toxic symptoms in dysentery. Rokitansky believed that dysentery began as a very superficial inflammation of the mucous mucosa, a simple catarrh, although the typical dysenteric lesions were not encountered until the membranous condition had appeared.

After the discovery of B. dysenteriae and its toxins many experiments were performed on animals to explain the mechanism of infection in bacillary dysentery and to discover the reason for the localization of the intestinal and nervous lesions. Practically all of these attempts have been made with either the cultures or the toxins of B. dysenteriae (Shiga). The results, however, are probably equally applicable to infections with B. dysenteriae (Flexner) if the nerve paralyses produced by the Shiga exotoxin (neurotoxin) be disregarded for nerve lesions caused by Flexner infection are rare (442).

Susceptible animals

The rabbit has been the animal generally used for these experiments. If cultures of the Shiga bacillus or its toxins (119) are injected subcutaneously, intravenously or intraperitoneally into a

rabbit, a fatal diarrhea usually develops. This is in striking contrast to the absence of characteristic reactions to injections of B. dysenteriae in cats, mice and guinea pigs. The resulting anatomical lesions of the intestines and nervous system are more or less identical with those to be described in man (vide infra). Dogs will develop ulceration of the intestines following injections of Shiga toxin (121) but not after feeding with toxins or cultures although they may succumb to diarrhea. A case of naturally acquired Shiga dysentery in a dog has recently been reported (408). Both large and small varieties of monkeys are susceptible to infection with B. dysenteriae (Flexner) for an epidemic of dysentery has been reported (225) among monkeys in a zoo. The infection orginated from an orangoutang, which arrived ill from the East, and spread to chimpanzees, macaques, and rhesus monkeys and finally to the keeper and his wife. B. dysenteriae (Flexner) was isolated from both animal and human stools. Serious epidemics of clinically and pathologically typical bacillary dysentery have been reported (443) among lambs, but dysentery bacilli have not been isolated.

Conradi (117) produced diarrhea, collapse and paralysis followed by death in rabbits by injecting a large dose of a toxin made by allowing a dysentery culture to autolyse. In four rabbits which survived longer than twenty-four hours there was a diphtheritic membrane of the intestine accompanied by ulceration. Vaillard and Dopter (121) by similar methods found that if the rabbits died in eighteen to twenty-four hours following small subcutaneous doses of toxin, the lesions were in the small intestine but with larger doses the lesions were in the large intestine. With injections of a preparation of dysentery bacilli ground under liquid air and extracted with saline, Lüdke (226) reported that the lesions were chiefly in the small intestine and but rarely in the large intestine. Kikuchi (227) injected the peritoneal exudate of guinea pigs who had had injections of dysentery bacilli, into rabbits and noted that paralysis was the main result. The chief discrepancies in experimental results with dysentery toxin may perhaps be due to the failure to distinguish between the endotoxin and exotoxin of the Shiga bacillus.

Nervous lesions due to exotoxin (neurotoxin)

Dopter (228) made the first comprehensive study of the effect of dysentery toxin on the central nervous system. He found in rabbits after subcutaneous inoculations of twenty-four hour broth cultures of the Shiga bacillus, or of culture filtrates, that serious lesions might occur in any portion of the nervous system although the medulla was most often affected. The gray matter, and almost exclusively the anterior horns, showed chromatolysis of the nerve cells in a varying degree and occasionally areas of necrosis in which the cellular elements and myelin fibers were destroyed so that scarcely a vestige of them was left. At the same time there was an intense hyperemia, and even hemorrhages might invade the tissue. The white matter was intact. In short, the lesion was that of an acute myelitis, often an anterior poliomyelitis and sometimes a polioencephalitis as well. In addition, Olitsky and Kligler (119) described a perivascular infiltration of small round cells either as a single layer about the sheaths or actually in the sheaths of the vessels of the brain and spinal cords of rabbits who had received exotoxin intravenously. Less frequently these round cells were present as a dense heaped up infiltration about the arterioles and capillaries of the central nervous system especially of the medulla and cervical cord and only slightly of the lumbar cord. These authors, working with exotoxin that had been carefully separated from the endotoxin, stated that a sublethal dose injected intravenously in rabbits resulted in the development of paresis or paralysis of the extremities in two to four days. Both anterior and posterior extremities might be affected; the former more frequently. This paralytic or paretic stage might endure for one to three days and might then be followed by complete recovery. Although the animal might be apathetic, have no appetite and lose weight, yet there were no intestinal symptoms. A lethal dose injected intravenously resulted in paralysis and prostration within twenty-four to forty-eight hours. There was considerable loss of weight. Involuntary evacuations of the bowels occurred but were without blood or mucus. There were no intestinal lesions at autopsy. The incubation period depended on the dose.

Ellinger and Adler (229) believe that the principal action of the neurotoxin is on the heat-regulating and vasomotor centers. Ani-

mals became poikilothermous after injections of exotoxin. If the body temperature fell very low the animals were unable to compensate in any way. With this fall in temperature the respiratory center was injured and this led to the death of the animal.

Intestinal lesions due to endotoxin (enterotoxin)

Olitsky and Kligler (119) with intravenous injections of a sublethal dose of Shiga endotoxin free from exotoxin produced diarrhea, loss of weight and subnormal temperature in rabbits after twenty-four to forty-eight hours. The stools were frequent and mucoid and occasionally blood-tinged. This state, during which no nervous symptoms occurred, endured for two to three days after which gradual recovery took place, or death followed. If a larger but still sublethal, or a lethal dose was injected intravenously, the animal reacted within twenty-four hours with subnormal temperature, considerable loss of weight and prostration. Severe diarrhea resulted, the stools being fluid and containing much mucus and more or less blood. The sensory and motor functions appeared normal. This state lasted for one to three days after which recovery took place or death followed. At autopsy the peritoneum was dull and its blood vessels injected and the peritoneal cavity contained a serous fluid. The small intestines were usually unaffected except that the vessels in the serosa might be injected. Occasionally the ileum was involved in the same extensive way as the large intestine. The walls of the latter were greatly thickened, edematous, injected and showed small discrete hemorrhages. A glairy gelatinous material covered the serous coat. On opening the intestines, the contents were found to consist of blood tinged mucus. The villi were hyperemic, the mucosa was swollen and revealed discrete hemorrhages and small ulcerations. In some instances necrotic areas were seen, and in one instance an area 2.5 cm. wide encircling the cecum was gangrenous. Microscopically, destruction of the glandular elements, as well as a superficial general necrosis was noted. There was a cellular exudation in the submucosa and considerable edema and degeneration of the muscular layers. There were no lesions in the cerebrospinal nervous system. Hence this poison can be regarded as an enterotoxin, in contradistinction to the exotoxin which is a neurotoxin.

The intestinal lesions were studied by Flexner and Sweet (120) who stated that rabbits were not subject to infection with dysentery bacilli when they were fed by mouth or when the cultures were injected directly into the abdomen. They noted no effect when an autolysate of Shiga cultures, which is largely endotoxin, was fed *per os* or even injected into the duodenum, so it was assumed that dysentery bacilli and their toxins could not produce intestinal lesions in rabbits by mere contact with the mucosa. They believed that although man undoubtedly absorbed dysentery toxin from the intestines where it was produced by the bacilli, yet rabbits had no such power of absorption. Dysentery toxin is destroyed by pepsin and more slowly by trypsin yet this did not explain the absence of intestinal lesions when toxin was fed by mouth. They could produce intestinal lesions only when the dysentery toxin was injected intravenously, subcutaneously or intraperitoneally. These lesions varied in intensity. The coats of the large intestine were greatly thickened by inflammatory edema. The mucosa was yellowish white and thrown into deep folds and corrugations. Occasionally more or less hemorrhage was associated with the edema. In some of the animals the transverse folds of mucous membrane were affected chiefly; they were swollen, the edges were hemorrhagic and a pseudomembrane was scattered over the surface. The hemorrhage in some cases extended into the serous coat. They believed that the character of the histological lesions in the cecum of these rabbits pointed to an action upon the substance and not primarily upon the surface of the intestine.

After dysentery bacilli were injected intravenously, they were found in the bile so these authors cut the bile ducts to prevent the direct action of the bacilli on the intestinal mucosa and after injecting dysentery bacilli found that the intestinal lesions were negligible but the rabbits died of nervous lesions (neurotoxin). This was analogous to the findings in mercurial colitis. When fatal doses of mercury were injected into normal rabbits, the cecum and the first part of the colon were the seat of hemorrhagic necrosis, and diphtheritic and ulcerative lesions, whereas in rabbits with biliary fistulae the changes in the cecum were much less intense. Flexner and Sweet (120) therefore concluded that the intestinal lesions were the result of repeated excretion of bacilli and toxins with the bile and also through

the intestinal mucosa of the large intestine especially at the cecum and that they were not due to the direct contact of the bacilli and their products with the mucosa.

Besredka (230), however, has recently shown that when B. dysenteriae (Shiga) and its toxins came in contact with the intestinal mucosa an erosion was formed. He fed one series of rabbits with cultures of living dysentery bacilli and another with killed organisms. Intestinal lesions were produced in both series. Dysentery bacilli did not give rise to septicemia when injected intravenously but pure cultures of these organisms were obtained from the bile and intestinal contents from the duodenum to the distal end of the small intestine. The blood, urine and organs remained sterile. The intestinal lesions were the same whether living bacilli, bacilli killed by heat, or endotoxin were injected intravenously, subcutaneously or fed by mouth. The intestinal lesions following intravenous injections of bacilli or toxins were the most severe, those after feeding by mouth the least severe and after subcutaneous injections they were midway. Following subcutaneous inoculations the bacilli at first remained localized and underwent a certain amount of autolysis. The surviving bacilli were then taken up by the circulation and transferred to the mucosa of the small intestine. The severity of the lesions depended upon the directness of the route that the virus traveled from its entrance into the body and its consequent diminution. The general resistance of the animal as well as the size of the dose injected determined whether death or survival would result.

If it is true that intestinal lesions are produced in rabbits by the contact of dysentery bacilli and toxins with the mucous mucosa, the mechanism of infection and the localization of the intestinal lesions in dysentery is very simply explained. These observations of Besredka (230) would seem to substantiate the views of Rokitansky (224) that the initial catarrh of the mucosa in dysentery was due to a direct chemical action starting from the surface, as well as those of Virchow (223) that the transition from the catarrhal to the diphtheritic membrane stage occurred in the cecum and colon because the intestinal contents remained and were in contact with the mucosa at these points the longest time. That Flexner and Sweet (120) did not find intestinal lesions following contact of toxin and mucosa

might be explained by the smallness of the dose, for Besredka, in one series of rabbits to which a small dose of toxin was fed, failed to find intestinal lesions. The reduction of the severity of the lesions in rabbits with biliary fistulae is explained by the fact that after intravenous inoculations of toxin, this toxin is excreted by the bile and as the bile ducts were cut the toxin could not reach the mucosa. Besredka, Flexner and Sweet all assumed that the intestinal mucosa excreted toxin and bacilli but it would seem possible that the bile is the chief if not the only means for the virus to reach the intestines from the blood. The production of the intestinal lesions could then be explained by the contact of the mucosa and the toxin as it passes downward from the opening of the common bile duct. This would not necessitate the assumption that the lesions of dysentery are produced by the excretion of the toxin through the intestinal mucosa.

Besredka's theory of intestinal immunity

Besredka (230) as a result of his work suggested that the immunity against bacillary dysentery conferred by one attack of the disease or by prophylactic vaccination was due essentially to the sensitization of the intestinal mucosa to dysentery bacilli and that the antibodies of the blood had a small rôle, or none at all, in the protective mechanism. He based this theory on the fact that the feeding of killed dysentery bacilli (heated vaccine) to rabbits produced agglutinins in the blood. Subsequent feeding of large doses of living dysentery bacilli was harmless for these rabbits although fatal for control animals. The serum of the rabbits who have had this prophylactic feeding of killed dysentery bacilli, however, would not protect other rabbits against feedings of live dysentery bacilli. Moreover subsequent feedings of killed dysentery bacilli to these immunized rabbits did not markedly raise the agglutinin titre of the blood. Besredka's (230) explanation was:

> That the preliminary feeding of killed dysentery bacilli produced an erosion of the intestinal mucosa by contact and when this healed the immunity was complete and subsequent feeding of lethal doses of living dysentery bacilli would not produce death, or feedings of killed dysentery bacilli would not increase the antibody titre of the blood for the sensitized intestinal barrier was impassable. The reason that the antibodies of the blood had

been looked upon as an index of immunity was because previous methods of prophylactic vaccination had been by subcutaneous and intravenous inoculations. These antibodies, however, merely indicated that there had been a systemic reaction to the vaccine. The real immunity, however, depended upon the excretion of the vaccine with the bile into the intestine and the consequent erosion of the mucosa, healing and immunity. By oral vaccination, immunity was produced without this systemic reaction.

Some doubt has been thrown upon this theory by Zingher and Soletsky (441) who were unable to produce immunity in rabbits by giving them B. paratyphosus B. by mouth in accordance with the plan outlined by Besredka (230). Kanai (445) found that the immunity produced in rabbits by the oral administration of Shiga vaccines was inferior to that produced by subcutaneous inoculations.

V. PATHOGENESIS OF BACILLARY DYSENTERY IN MAN

The mechanism of the production of the lesions of human bacillary dysentery is doubtless similar to that described by Besredka (230) in experimental dysentery in rabbits. The dysentery bacilli in practically all instances are taken into the mouth with food or drink and pass directly to the intestines. There is no evidence that dysentery is primarily a septicemia such as is typhoid fever. The organisms can be cultivated at autopsy from the whole length of the colon and even from the small intestine (120) where there may be no pathological lesions but owing to the peristalsis of the small intestine, a prolonged lodgment of bacilli there in any great numbers is prevented and it is not until the cecum and colon are reached that the organisms have an opportunity to multiply appreciably and produce toxins.

The breaking down and autolysis of the bacterial cells (both Flexner and Shiga varieties) liberates an endotoxin. This endotoxin is a local irritant. To it are to be ascribed the great majority of the intestinal lesions. It may doubtless cause hyperemia alone. It may cause a catarrhal, an ulcerative or a pseudomembranous type of inflammation. Not only is the mucosa affected but also the submucosa, the muscularis and in a few cases even the peritoneal covering. There is an exudation of lymph and cells into the intestinal coats. It is the edema of the submucosa that causes most of the thickening of the intestinal wall. This may be double that in health. The mucous

membrane may be only hyperemic with an excess of mucus or it may have superficial ulcerations upon the summits of the rugae. It may be covered by a false membrane. In long standing cases the ulcerations may be numerous and confined almost entirely to the lymphatic elements of the intestinal wall. Deep ulceration is not very common in children even after the pseudomembranous type of inflammation.

Bacillary dysentery does not always involve the whole length of the colon even in cases proving fatal in the acute stage, but when only a portion of the intestine is attacked that part will be more or less uniformly affected and no extensive and abruptly defined healthy areas will remain within it, as is so commonly the case in advanced amebic dysentery (3). This difference is perhaps due to the different mechanism of infection in these two diseases. In the former, the lesions are probably the result of the direct contact of the mucous membrane with the endotoxin which diffuses uniformly in the area in which it is liberated. Amebae, on the other hand, may attack the intestinal wall singly or in groups and thus leave healthy areas between the erosions.

As a rule the ulcerations of bacillary dysentery are numerous and have clean surfaces, elevated edges and a base formed by the submucosa. In contradistinction to the ulcers of amebic dysentery, the edges of the ulcers of the bacillary variety are not undermined. The borders are irregular, reddened, swollen and infiltrated. The ulcers of bacillary dysentery in adults may be very extensive leading to the separation of large sloughs, or may extend deeply into the coats of the bowel, causing in extreme cases gangrene, (400) perforation (403) and peritonitis or in less serious cases inducing the exudation of much lymph into the peritoneal coat subsequently producing adhesions. Actual suppuration of the intestinal wall never occurs in uncomplicated cases of bacillary dysentery. However, mucous cysts and submucous abscesses of the wall of the large intestine may occur in chronic cases (374). The ulcers heal with the formation of connective tissue leaving a scar in the mucous membrane that is often pigmented. Many bacilli and cocci are found in the inflamed mucous membranes and are especially numerous in the necrotic portions. In the deeper layers the bacilli are found in small numbers, but in

the glands, between the gland cells and in the glandular stroma they are very numerous. Cocci are not as a rule found in these latter locations. In the submucosa and often in the muscularis the cell infiltration is accompanied by numerous bacilli. Cultures from these regions have shown the presence of B. dysenteriae in pure culture (77).

What part organisms other than dysentery bacilli play in the production of intestinal lesions is hard to say. It is probable that pyogenic cocci—streptococci chiefly (39)—multiply in the necrotic tissue that results from the local irritation of the dysentery endotoxin. Whether they actually attack the intestinal wall it is impossible to state. Doubtless they play an important part in the production of pus which is often present in large amounts in the exudate and stools.

During the early stages of bacillary dysentery, there is a marked febrile reaction. This is probably the result of a systemic reaction to absorbed endotoxin, as well as to the "cleavage products" that may be absorbed from the necrotic intestinal mucous membrane. It would seem justifiable to assume that this absorbed endotoxin is excreted into the intestines again with the bile as Flexner and Sweet (120) and Besredka (230) have shown to be the case with dysentery toxin that has been introduced parenterally in rabbits. The active peristalsis of the small intestine probably prevents the endotoxin from remaining there long enough to produce irritation of the lining of the jejunum. As with the originally ingested bacilli, it is not until the lower ileum and colon are reached that there is sufficient stasis for the excreted endotoxin to produce dysenteric lesions. This absorption of the endotoxin from the colon and its excretion by the bile thus form a vicious circle.

If the lesions of bacillary dysentery were the result of the excretion of this absorbed endotoxin by the intestinal wall as Flexner and Sweet (120) suggested, the distribution of the lesions would be related to the blood supply and they would probably be more numerous at the attachment of the mesentery. This does not appear to be the case.

The Peyer's patches of the ileum are unaffected or only moderately swollen in bacillary dysentery. The solitary lymph nodes in the

small intestine may be hyperemic and swollen though they are rarely ulcerated, thus contrasting with the frequency of the ulceration of these nodules in the large intestine.

The severity of the damage to the intestines evidently depends upon the virulence and the endotoxin producing properties of the infecting organism. In patients dying of the so-called "terminal dysentery" (3, 138) in whom malnutrition, scurvy, rickets, pneumonia or other disease is more responsible for death than the dysenteric infection, the intestines may merely be hyperemic or have slight ulceration of the lymph follicles of the colon and lower ileum. The length of the illness does not necessarily determine the severity of the lesions for ulceration and membrane formation are not unusual in infants dying of bacillary dysentery of but a few days duration.

The most essential difference between the lesions of typical acute and chronic bacillary dysentery (which is practically confined to adults) is in their extent. In the former, the whole, or nearly the whole, length of the colon and often also the lower part of the ileum are uniformly involved in an acute inflammatory process which may rapidly prove fatal. In the latter, the process is usually limited to the lower half of the colon and the patient survives long enough to allow of more extensive destruction of the mucous membrane of the affected areas, which presents a worm eaten appearance. The character of the lesion differs mainly in that the earlier fibrinous changes in the mucosa have usually disappeared in the chronic stage and only very extensive irregular depressed ulcers are left which usually run into one another with some general thickening of the mucous membrane. In some instances the intestinal wall may be found to be gangrenous along part of its course, (400, 403). In keeping with this long period of intoxication, the wall of the intestine as well as other organs sometimes shows amyloid change (39).

In infections with the Shiga bacillus the *central nervous system* (228) may be the seat of lesions due to the prolonged absorption of exotoxin to which B. dysenteriae (Shiga) gives rise, as a product of its growth, in the intestine. However, as man seldom absorbs as much exotoxin from his intestines as is usually injected experimentally into a rabbit, these lesions are rarely fatal. Consequently there are but few reports of the postmortem examinations of the brains and

spinal cords of patients who have died of paralysis following Shiga dysentery. The findings that have been published (343) are similar to those seen in experimental Shiga infections in rabbits, and are analogous to those of poliomyelitis and encephalitis.

VI. CLINICAL DATA IN ADULTS

Hippocrates'[1] original statement that dysentery was a condition characterized by the frequent passage of stools containing blood and mucus, accompanied by straining and tenesmus, has not been improved by any later clinical description. A provisional diagnosis of dysentery is justified with that fundamental picture. Not until the advent of laboratory methods could this syndrome be divided into bacillary and amebic dysentery, typhoid, paratyphoid, cholera and food poisoning. The demonstration of the relationship of liver abscesses to amebic dysentery rendered it possible to diagnose many cases of amebic dysentery without stool examinations but not only do mixed amebic and bacillary infections (46, 60, 355) occur but all liver abscesses are not due to amebae (234) so that reliable cultural methods are usually necessary for a final diagnosis.

Typical cases of amebic and bacillary dysentery, typhoid, paratyphoid (394, 206, 235), cholera and food poisoning present characteristic clinical pictures so that when seen side by side they can, as a general rule, be distinguished. However, it must be remembered that even in the presence of an epidemic of any one of these diseases it occasionally is impossible, without laboratory confirmation, to state that an individual case is of the prevailing type. Among a number of cases sent back from the Dardanelles as amebic and bacillary dysentery I have found some due to infection with B. paratyphosus B, although clinically they were indistinguishable from the remainder of the convoy.

Inasmuch as we have effectual specific remedies for amebic and Shiga dysentery (in adults), an accurate laboratory differentiation of these cases of bloody diarrhea is most essential. Clinical appearances alone are not reliable.

Incubation period

The time from the initial ingestion of the dysentery bacilli until they have become sufficiently numerous to produce enough toxin to cause clinical symptoms may vary from one to eight days. Dysentery bacilli probably multiply rapidly in the intestine but cultures of the stools rarely show viable dysentery bacilli in great numbers. One to ten colonies for each gram of faeces cultured is a high number even in severe cases. This may be due to the great acidity of the stools that occurs in bacillary dysentery (371, 382), or possibly is a result of d'Herelle's phenomenon (125). Great numbers probably die and autolyse in the intestine and thus liberate a large amount of endotoxin. This endotoxin has two effects; one local, due to contact with the intestinal mucosa according to Besredka (230) and the other systemic due to absorption into the blood stream. The length of the incubation period probably depends upon the quantity and the virulence or toxin producing properties of the infection bacilli that were originally ingested. Lemoine (236) reported a case of twenty-four hours' incubation in which infection occurred via the rectum from the use of a chamber containing dysenteric stools although the soiling of the fingers at stool cannot be excluded. In one instance (231) a culture of the Shiga bacillus came in contact with the conjunctiva and dysentery resulted within twenty-four hours. It is well known (232) that bacteria quickly pass from the conjunctiva to the nose and throat. Laboratory infections of twenty-four to forty-eight hours incubation were observed by Flexner (39), Strong (112) and Kruse (34). In an epidemic caused by river water in a Japanese village (46) the incubation period was in most cases from four to five days.

Onset

The prodromal symptoms of general malaise, fever and headache, that are frequently present during the latter part of the incubation period, are probably due to the systemic reaction to the foreign protein of the absorbed endotoxin. The loss of appetite and nausea either may be due to the same cause or are possibly reflex from the local irritation of the intestinal mucosa by the endotoxin. Frequently there are no prodromata and all of the symptoms are attributable to

the local effect of the endotoxin. The onset is usually characterized by a griping pain in the abdomen and an urgent desire to defecate, resulting in the passage of ordinary formed feces, which temporarily relieves the pain. The pain, however, soon returns, usually in the umbilical region although other locations are frequent, associated with a desire to defecate and the passage of stools which are now of softer consistency and may be streaked with blood. These attacks are repeated at decreasing intervals so that the patient is more or less continuously at stool. Frequently the stools contain nothing but blood and pus. They are usually acid in reaction and Jacoby (371) believes that this is of diagnostic importance. The griping pains in the abdomen are doubtless due to the passage of the intestinal contents over the inflamed mucous membrane. They may become very intense in severe cases and are plainly distinguished from true tenesmus, the bearing down pain experienced in the rectum during and for a time after the actual evacuation of the bowels. Straining and griping are quite constant features. Tenesmus is commonly associated with dysenteric lesions in the rectum, which usually occur early in the disease. Prolapse of the rectum and consequent incontinence of feces may occur in severe cases with marked tenesmus.

In a choleraform type of bacillary dysentery described by Castellani (7), the onset is sudden, with rice water or serous stools; the patient may vomit and usually becomes rapidly worse. Blood may occasionally appear in the stool. The infecting bacilli in these cases are probably exceedingly virulent and rapidly produce a potent toxin so that the maximal effect is noted early.

Many afebrile cases of non-bloody, non-mucous diarrhea of but twenty-four hours' duration have been proved (57, 58) to be due to infection with dysentery bacilli. The so-called epidemic diarrhea is usually mild dysentery (413). These cases may occur during epidemics of typical dysentery and so be diagnosed but frequently they are sporadic and occur during the winter months. The attack may in no way differ from an ordinary attack of diarrhea due to other causes. In the Northern cities of the United States, the majority of the cases occur sporadically and are of this type. Extensive epidemics, even in asylums, and severe cases are the exception. These isolated cases are frequently overlooked unless the bacteriologist as

well as the clinician diligently searches for them. In one large hospital but eight cases of bacillary dysentery were diagnosed in eight years, yet in one month when repeated stool cultures were done on all patients with diarrhea, two cases of Shiga infection and one of Flexner infection were discovered. It is probably through these sporadic, mild and frequently undiagnosed cases that bacillary dysentery is often spread (117).

The term pseudodysentery that is sometimes applied to these mild cases of dysentery would seem to be not only superfluous but also misleading. They are just as much true dysentery bacteriologically as the more severe types and, if they are not clearly recognized as such, are dangerous from the public health point of view. These mild cases are due in all probability to dysentery bacilli that produce but a small amount of toxin, so that there is only a catarrhal inflammation of the mucous membrane of the intestine without erosion.

Course

As a rule, the *stools* become slimy and bloody on the second or third day and very soon are composed of pure blood and mucus. Later the mucus becomes thick and colorless with less blood and finally there is the mucopurulent stool so characteristic of bacillary dysentery. The stools are usually small. They have a stale, spermic odor and are generally not offensive. In the severe cases, however, they may become exceedingly foul and contain pus. It is possible that this represents a secondary infection by streptococci or other pus producing organisms. Extremely foul stools are an unfavorable sign. Not infrequently the endotoxin may be so destructive that shreds of mucous membrane and occasionally tubular sloughs (39) may be passed by rectum. In early bacillary dysentery the usual number of stools is from six to fifteen per day. It is impossible in most cases to distinguish the amebic and bacillary varieties by the gross appearance of the stools. Microscopic smears of the stools (222) may be of assistance in diagnosis. If there are no amebae and many cells, the infection is probably bacillary (399). There are, however, many large phagocytes that resemble amebae in the stools of patients with bacillary dysentery. Early in the course of bacillary dysentery smears of the mucus contain a fair number of cells most of

which are epithelial with some mononuclears and polymorphonuclears. Red blood cells are in clumps and scattered throughout the smear. Later in the disease, the cells increase and are predominately polymorphonuclear.

The *urine* diminishes in amount and at times may contain a trace of albumin. Urination may be painful (dysuria) (39) when the rectum is markedly affected by the endotoxin. Thirst is rarely present in mild cases but in severe ones due to the loss of body fluid, it may become marked.

Vomiting is relatively unusual in mild cases. The *tongue* is usually coated with a white fur. *The temperature* in all but the very mildest cases rises to 101° to 104°F. In mild cases the febrile curve may be intermittent throughout but it often assumes a remittent type for the first few days and gradually declines to normal in the morning while still rising to 100° or 102° in the afternoon. There seems to be no relation between the temperature and the severity of the intestinal lesions (55). A slight return of fever after the curve has been normal for a time is almost always accompanied by an exacerbation of the symptoms except in serum treated cases, when the elevation may be due to serum sickness. As convalescence becomes established, the temperature often becomes subnormal. The *pulse* increases in frequency and in the more severe infections becomes very small. In adults, if the patient is to die, the stools become serous, the pulse rapid and irregular, the temperature drops to subnormal, the number of stools may diminish, hiccough appears and death due to exhaustion generally occurs during the second or third week.

If lesions are present in the upper portion of the colon or in the small intestine, various intoxication symptoms appear, such as headache, general malaise, muscular pains, sleeplessness, numbness and stupor. Delirium is rare except as a terminal symptom. The clinical picture may simulate that of typhoid fever. As a matter of fact, in many of these cases, B. typhosus as well as B. dysenteriae has been isolated (237). I have encountered cases of bacillary dysentery in troops that have become secondarily infected with B. paratyphosus B. (68). Under conditions in which trained nurses are scarce, it is relatively simple for these mixed infections to occur (207) and the possibility should always be considered.

Physical examinations are usually of no diagnostic importance. Extreme emaciation, atrophy of the general muscular tissues, Hippocratic facies and a retracted, scaphoid and tender abdomen are striking features in cases of long duration. On careful palpation, the thickened bowel may at times be felt, but usually the abdomen is too tender to allow such manipulation. The tenderness is especially acute over the course of the colon. The spleen is not enlarged except in very severe cases (344) or unless malaria, typhoid or other diseases coexist (55).

Severe *hemorrhage* from the bowel is less common than in the amebic form, but Rogers (3) reports the fatal loss of blood from a deep ulcer in the upper part of the rectum in chronic bacillary dysentery.

In occasional cases instead of diarrhea, *constipation* may be the predominating symptom for the disease may be limited to the lower bowel, and feces may be accumulating in the higher region of the colon—a condition which may be recognized by distention. Shiga (77) describes an ascending variety of acute dysentery, which, beginning in the rectum, spreads upwards along the large bowel.

Nervous symptoms

The nervous symptoms due to the Shiga exotoxin are not constantly present in all cases of Shiga infections. This may be due to the fact that the effects of the exotoxin are manifest later in the disease than those of endotoxin. The former must be absorbed into the blood and then probably be accumulated in the nervous tissues to produce sufficient lesions to give rise to clinically detectable nervous symptoms. In many severe cases the patient succumbs to the intestinal lesions before the exotoxin has had time to produce lesions in the central nervous system while in many mild cases in which the dysentery bacilli produce toxin in small amounts the patient has time enough to manufacture antiexotoxin to neutralize the exotoxin before it has sufficiently accumulated in the nervous tissues to produce paralysis. *Peripheral neuritis* is the most common condition caused by the exotoxin. It is generally mild and often confined to one nerve (55, 338). Schlesinger's (240) work would indicate that this neuritis is due to the slow effect of absorbed dysentery toxin similarly to

the nerve lesions in diphtheria, for he reported *polyneuritis* in twenty soldiers after the dysentery bacilli had disappeared from the stools. *Paralysis*, chiefly paraplegia, is occasionally reported (52, 274, 338).

Recovery

Recovery takes place as soon as the body can produce sufficient antiendotoxin to neutralize the endotoxin and thus prevent further destruction of the mucosa. Besredka (230) believes that the protective mechanism does not involve the antibodies of the blood but that the intestinal mucosa itself, after the erosion caused by the endotoxin has healed, becomes sensitized to dysentery bacilli and acts as a barrier against further infection. That may be true, but it would seem impossible to avoid the assumption that an antiendotoxin must be formed by the blood or other antibody forming center, to neutralize the endotoxin and allow the erosion to heal. Bacteriocidal bodies evidently are not essential to recovery for although dysentery bacilli usually disappear from the intestines a few days after the cessation of the acute symptoms yet some patients after recovery from dysentery may harbor these bacilli in their intestines for months and even years without symptoms. Although these carriers have sufficient antiendotoxin to prevent dysentery bacilli causing inflammation and erosion of the intestinal mucosa and although bactericidal bodies are demonstrable in their sera, yet the mere fact of the continued presence of dysentery bacilli in the stools would seem to indicate that bactericidal substances are not essential. However, as persistent carriers of dysentery bacilli are the exception, the bactericidal bodies may be excreted into the intestines of the majority of patients and account for the disappearance of dysentery bacilli from the stools after recovery. These findings are comparable to those of individuals who become chronic carriers of diphtheria bacilli after convalescence from the disease. The part played by d'Herelle's (125) "bacteriophage" or Kabeshima's (127) bacteriolytic ferment, in determining the patient's recovery is impossible to state at present, (vide supra).

The *duration* is four to eight days in light cases and three to six

weeks in those that are severe. Shiga (46) found an average duration for all cases of 40 days under medicinal treatment and 25 days under serum therapy. During recovery the stools regain their fecal consistency, the number lessens, and the appetite and strength begin to return. *Relapses*, however, are common, due to dietetic errors, exposure and allowing the patient to get up from bed or to resume a general diet (222) too early.

Reinfections, except for relapses (58), are rare in bacillary dysentery. Shiga (77) noted but four cases among 10,000 patients. However, during mixed epidemics, a convalescent from Flexner dysentery may acquire a new infection with Shiga bacillus (57, 69, 138, 140, 202) and vice versa.

Chronicity

Bacillary dysentery in adults has often been divided into two types, the acute and the chronic. The latter is usually, though by no means always, due to infection with B. dysenteriae (Shiga). Sonne (238) states that the Flexner bacillus was found mainly in mild and sporadic cases. Remlinger, (65) however, reported a severe Flexner epidemic in the Argonne. Many physicians report that no clinical difference can be detected between patients infected with Shiga and Flexner bacilli (69, 140). Moreover, the Shiga and Flexner bacillus may often exist in the same patient (57, 69, 138, 140, 202). Inasmuch as the chronic cases begin in a manner similar to those that are acute, this differentiation is not distinct. Chronicity is perhaps better described as a complication of dysentery rather than as a distinct variety.

Although the acute stages insensibly merge into the chronic disease, so that no definite line can be drawn between them, yet for purposes of analysis Rogers, (3) has taken a duration of one month or more to indicate chronicity. As a general rule, bacillary dysentery terminates in either death or recovery within a few weeks, and but comparatively rarely lingers on with longer or shorter remission for several months, as is not uncommonly the case with inadequately treated amebic disease. Some observers (260, 402, 409), however, have reported that 5 per cent of all cases of dysentery become chronic.

Chronic dysentery in children is extremely rare. The remissions are not so complete and lengthy in the bacillary type as in the amebic variety, the disease tending to run on unchecked until the patient eventually develops some immunity to the infection and slowly recovers, or, worn out by his sufferings, succumbs to exhaustion, inanition, steady loss of body fluid or to some intercurrent infection.

Dysentery carriers

There is no definite division of convalescent dysentery patients, whose stools continue to harbor B. dysenteriae, into chronic cases and persistent carriers. Fletcher and MacKinnon (175) in a recent study of 1782 British soldiers convalescent from dysentery, some of whom gave histories of intermittent dysentery dating from the Boer War, found 74 still excreting dysentery bacilli. The average *Flexner* carrier was in good health, his stools were formed and free from blood and mucus. He was fit to carry on his work unless subjected to very adverse conditions of feeding, temperature or labor which might induce attacks of diarrhoea. The *Shiga* carrier, on the other hand, was generally an invalid, his stools usually contained blood and mucus and he had frequent attacks of diarrhoea. Furthermore, he often became a mental wreck. Cases of this chronic carrier state, lasting from two to ten years, have been noted. Arnheim (187) regarded the Shiga carriers as the more important. Other Germans (73) stated that Flexner carriers were too numerous to quarantine. The number of dysentery carriers found appears to depend on the epidemic and also possibly on the conditions under which the bacteriologist must work. The usual percentage is rarely more than one per cent (151, 186, 239) but one author reported that 13 per cent of his convalescent patients became carriers of the Flexner bacillus (75).

One investigator (186) suggests that B. dysenteriae in chronic carriers may lurk in the bile as is frequently found to be the case with B. typhosus carriers. Brückner (214) in an autopsy on a dysentery carrier who died of an intercurrent infection, found Flexner bacilli in the small bile ducts in the liver. There were no intestinal lesions. Others (213), however, reported that bile had a destructive and restraining influence on B. dysenteriae both in the intestine and in vitro. Hannon (342) has shown that bile salts were inhibitory to the growth of dysentery bacilli.

Complications

Perforation and gangrene of the colon and *peritonitis* are rare (241, 400, 403) although the abdomen may be sufficiently tender and rigid to simulate these conditions. However, in 108 fatal Civil War cases studied by Woodward (52) perforation occurred in eleven.

The incidence of *liver abscess* and portal pyemia is negligible. Rogers (3) in 45 autopsies in Calcutta did not find a single instance.

Abscesses in other locations are occasionally reported. Shiga (46) noted one in a convalescent in the upper portion of the rectus abdominalis and in a second case in the gluteal region. The ischiorectal fossa may also be the seat of abscesses (7). They are probably due to secondary infections.

Arthritis. Sydenham (24) noted that dysentery was sometimes associated with rheumatic pains. A swelling of one or more of the large joints and inflammation of the tendon sheaths of a very obstinate character have been noted in certain outbreaks (39, 242) and as a sequel to bacillary dysentery during the Boer War (3). Arthritis of the knees and occasionally of other joints was not an infrequent finding in the cases during the Great War (55, 57, 64, 243, 403, 411, 421) both in untreated cases as well as those under serum therapy. Graham (360) stated that the usual time of onset was between the sixth and twenty-third day after the first symptoms of dysentery. There was no relationship between the time of onset of the arthritis and the severity of the dysentery. In severe cases there was considerable rise of temperature which might oscillate for weeks. In mild cases there was very little if any fever. The swelling and pain were usually though not always confined to one joint. It appears to be due to absorption of endotoxin from the bowel and its excretion into the joint cavities as is known to be the case during the absorption of toxins of septic and gonorrheal origin (244). Joint involvement occurs in both Flexner and Shiga infections. This arthritis tends toward recovery, without going on to suppuration, although it may take some months to resolve. Stiffness may continue for a long period but apparently always ends in complete recovery (360). Cultures of the fluid of these joints have with few exceptions (57) been sterile but the presence of agglutinins in these exudates has frequently

been demonstrated (55, 57), in some cases in higher dilution than in the blood serum of the patient.

Parotitis may occur in severe cases, and also in moderate cases which run a chronic course (46, 421). It is usually bilateral and appears during the third to the fifth week of the disease. Among 436 patients Shiga (46) found only eight instances of parotitis. The dysentery bacillus was never found in the pus and tissues removed. There is probably no connection between parotitis and the dysentery bacillus. It results from a secondary infection by other organisms present in the mouth (77).

Edema and *ascites* are often seen in debilitated patients or during convalescence (245) or during the terminal stages of protracted cases and are frequently combined with general anemic edema. Isenschmid (246) believes that the edema following dysentery, which is usually ascribed to weakness of the heart, is probably of the starvation edema type. Some of the instances of war edema (Kriegsoedema) seen in Germany were probably sequelae to bacillary dysentery (247). Oberndorfer (248) in autopsies on patients dying of war edema found typical lesions of dysentery in the large intestines.

Functional disturbances of the heart have been prominent in some epidemics (249, 250). Simple endocarditis is not infrequent (251) but the malignant form is rare. Myocarditis and pericarditis may occur in severe cases (251, 411).

Appendicitis has been cited (7, 421) as a complication during convalescence from bacillary dysentery. Vives and others (252), however, state that appendicitis is more frequent in amebic than bacillary dysentery.

Beriberi has been noted as a frequent complication in Japan (46) possibly due to the exclusive diet of rice water gruel so frequently prescribed in the East. The prognosis is not good.

Stenosis of the large bowel, more particularly of the sigmoid flexure, proctitis (403) and periproctitis (256), due to cicatricial contraction of the healing ulcers are among the most important though infrequent sequelae of dysentery as Cantlie (257) has emphasized. The symptoms are: constipation of insidious onset (sometimes alternated with attacks of diarrhoea) associated in due course with a sensation of distension in the abdomen, recurrent colic, loss of appetite, nausea

and vomiting. Stenosis of the intestines is a serious condition and must be energetically treated. A case of almost complete obstruction of the rectum (258) and a fatal case of intestinal obstruction following dysentery have been reported (259).

Suprarenal insufficiency and postmortem lesions of the suprarenal glands almost identical with those due to diphtheria toxin have been found during epidemics of severe Flexner dysentery (65, 69).

Chronic gastritis and *intestinal ulceration* with pain, meteorism, diarrhoea and dyspepsia (260, 353, 409) may follow dysentery. They are probably the result of direct and reflex irritation due to the cicatricial tissue of the original dysenteric ulcers rather than to a continued action of endotoxin. Alexander (261) found achlorhydria and apepsia in some of his patients after recovery from dysentery. Glaessner (361) has also reported a diminution of pepsin. He believes that the prognosis is more unfavorable in cases with a deficiency of pancreatic secretion and that this should be taken into account in treatment.

As *rare complications* (212, 251, 253, 338) of bacillary dysentery there may be pleurisy, thrombosis, acute and chronic nephritis (419), acute conjunctivitis (345, 346), cyclitis, iridocyclitis (360), iritis (411), prostatitis, rectal carcinomata (398), tetany from hemorrhage in the parathyroid glands (254), pyelocystitis (217, 218, 219), urethritis (345), vaginitis (347), meningomyelitis (362), hemorrhagic encephalitis (363), pyemic manifestations such as pylephlebitis, and meningitis (255). The presence of the last was probably a coincidence. Conjunctivitis was noted in a patient with a Shiga infection but as no dysentery bacilli could be isolated from the eyes, it was assumed to be due to Shiga toxin (346). Nolf (55) reported labial and nasal herpes in a large percentage of his cases (Flexner dysentery).

Blood

The blood picture is often of assistance in distinguishing amebic from bacillary dysentery. In the former *white blood cell counts* of from 20,000 to 40,000 are comparatively common (275) while in the latter, although a slight polymorphonuclear leukocytosis is frequent, the count rarely exceeds 15,000. In more severe Flexner infections Nolf (55) found the average number of white cells to be 25,000

predominately polymorphonuclears, rising to 47,200 in fatal cases. The leucocytosis disappeared as the dehydration decreased. Marcovici reported (410) that 60 per cent of acute cases had a moderate leukopenia, 6 per cent had a slight leukocytosis (up to 10,900 per cmm.) and that in 34 per cent the white blood count was normal. During convalescence the number of leukocytes was normal. In chronic cases there was usually a leukocytosis (up to 9,400) and occasionally an eosinophilia (3 per cent eosinophiles). He concluded that white blood cell counts were of but little assistance in differentiating dysentery from other forms of diarrhoea. Martinez (444) stated that in bacillary dysentery there was a polynucleosis but no increase in eosinophiles while in amebic dysentery there was a slight eosinophilia and there might be a mononucleosis. Helminthiasis induced a polynucleosis with eosinophilia.

Findlay (263) has recently reported the possibility of differentiating amebic and bacillary dysentery in 90 per cent of cases by the iodin reaction and the production of nuclear pseudopodia in the polymorphonuclear leukocytes.

The *red blood cell counts* are at first relatively increased from the drain of fluid by the bowel, but fall below normal if blood persists in the stools.

Differential Diagnosis, summary

A presumptive diagnosis of bacillary dysentery can be made in temperate climates or during epidemics when the patient has had a febrile onset, passes frequent bloody mucous stools and has colic, tenesmus, resistance over the large bowel, palpable thickening of the wall of the colon, and pain on abdominal pressure. It must be remembered that tenesmus is not a constant symptom because in the majority of instances it only exists when the rectum is affected. The presence of pus in the stool is strongly suggestive of bacillary dysentery (399). The diagnosis of the abortive form of dysentery, which often occurs sporadically in the winter, or in the beginning of epidemics, is very difficult. Similarly too, the diagnosis of dysentery simulating typhoid is not easy. Repeated microscopic examinations of the stools for amebae, and other parasites, numerous stool cultures for dysentery and other bacilli and probably of most importance,

studies of the agglutination reactions of the patient's serum (after the sixth day) with standardized methods should be undertaken in all cases. A cutaneous reaction for dysentery bacilli similar to the Shick test for diphtheria has been introduced (39) but its value has not been proved.

The conditions necessary for a *definite diagnosis* of bacillary dysentery are the isolation of the bacillus from the patient's stools or a positive agglutination reaction of the dysentery bacillus with his serum (after the sixth day) (235, 264).

Attention must be paid to exclude carcinomata, tuberculosis, polypi, syphilis of the rectum (265), hereditary syphilis (266), hemorrhoids, foreign bodies intussusception, mercurial poisoning, malaria (369), and pressure from uterine tumors (267) as causes of the discharge of blood and mucus from the bowel. Amebic dysentery as well as the cases of diarrhoea that may be due to balantidium coli (89, 90), lambia (91), trichomonas (92, 93) ankylostoma, schistosoma, paragonimus (265) chilomastix mesnili (364) or bilharzia (94) must be differentiated etiologically, clinically and anatomically from bacillary dysentery. It must not be forgotten, however, that mixed infections with amoebae or other parasites and dysentery bacilli may occur (46, 60, 355). The following are perhaps the most important points (46, 404) in the *differentiation of amebic and bacillary dysentery:*

1. The onset is usually acute in bacillary dysentery and gradual in amebic.

2. Amebic dysentery usually runs a chronic course.

3. In the amebic form, no dysentery bacilli can be found, except in the mixed infections of both amebic and bacillary dysentery.

4. In amebic dysentery, toxic symptoms such as high fever, general malaise, anorexia, rapid emaciation, or various nervous symptoms, are not usually observed.

5. In bacillary dysentery liver abscess is never present; it is a very frequent complication of amebic dysentery.

6. The diagnostic value of the emetine treatment. The failure of hypodermic injections of emetine to bring about very marked amelioration of dysenteric symptoms within two to three days is usually sufficient to exclude the presence of amebic disease and thus makes it

so extremely probable that bacillary infection is present as to indicate active treatment against the latter disease (3). However, emetine therapy is not devoid of danger, for deaths have been reported (268) from its toxic effects. This drug should only be given when the presence of amebic dysentery is suspected and not as a routine method of differential diagnosis.

7. The anatomical processes are also different. According to Kartulis (269) and Kruse (34) the edges of the ulcers are peculiarly undermined in amebic dysentery, while in bacillary dysentery this is never the case and the ulcers are situated on the surface of the folds of the mucous membrane.

VII. CLINICAL DATA IN CHILDREN

Infants and young children are much the worst sufferers from bacillary dysentery. When a household becomes infected, the adults may merely have a mild diarrhea often without blood in the stools, lasting twenty-four to forty-eight hours. The children on the other hand usually have a severe bloody diarrhea which is frequently fatal. In other words the same variety of dysentery bacillus may have but slight effect on the intestinal mucosa of an adult, possibly because of his acquired immunity, while in an infant the organisms usually produce marked inflammation with profound pathological changes. It is unfortunate that bloody diarrhea in children has not been more generally recognized as dysentery and that names such as summer diarrhea, infectious diarrhea and ileocolitis have been applied. Bacteriological studies (47, 48, 124, 138, 149, 150, 151, 153, 154, 215, 270) in many cities have repeatedly proven that the great majority, if not all cases, of bloody diarrhea in children are due to B. dysenteriae. Bacillary dysentery in children can be recognized in nearly all instances by the clinical data alone.

The onset is usually sudden, the first symptom being a loss of appetite, feverishness and irritability or drowsiness. Vomiting and convulsions are not infrequent during the first twenty-four hours. Within a few hours of the initial symptoms there is an increase in the number of stools. These are usually watery for the first day. Blood does not usually appear in the faeces until the second day of the disease. Within three or four days the stools consist almost entirely

of blood and mucus for the endotoxin has, by this time, produced a marked inflammatory reaction. The number of bowel movements ranges from three to thirty per day. After the first twenty-four hours, the individual stools are exceedingly small, perhaps a teaspoonful of mucus and blood passed after much straining.

A clinical diagnosis of bacillary dysentery is justifiable only when the patient has had an acute febrile onset and the passage of mucous and persistently bloody stools. Children who have diarrhea and have blood in their stools (usually bright blood) on only one or two occasions are usually not suffering from dysentery. The agglutination reactions and stool cultures show this. It is true, however, that infants whose stools contain much pus even without blood almost always have dysentery. Smears of the stool stained with methylene blue should be made to distinguish mucus from pus, for differentiation by the naked eye, is frequently exceedingly difficult. The presence of mucus alone in stools is not significant of dysentery.

Children with bacillary dysentery are usually quite ill and greatly prostrated. For the first few hours they are frequently restless and irritable. Later they become drowsy and apathetic. The appetite may entirely disappear. Loss of weight is rapid. If the stools are very loose for the first day or two and if there is a great disinclination to take water as well as food, dehydration may become a marked and important condition. The numerous and often painful bowel movements frequently make rest and sleep impossible without sedatives.

In most non-fatal cases the temperature falls to normal by the fifth to eighth day. The blood gradually disappears from the stools during the second week. The bowel movements become less numerous and assume a fecal character if the appetite improves so that food is taken.

If the child has been suffering from simple diarrhea or some other disease at the time of the infection with bacillary dysentery, the character of the onset is frequently masked. Usually, however, there is a history of a sudden rise in temperature followed by an increased number of stools containing blood and mucus. Mild non-bloody diarrhoea due to B. dysenteriae may occasionally occur in children as well as in adults.

With most of the cases in well nourished children who die in the early stages of bacillary dysentery as the result of an overwhelming intoxication, a pseudomembranous type of inflammation is found. Doubtless the process in the milder cases is catarrhal in type with or without superficial ulceration. Deep ulceration is found in protracted cases and is especially localized in the lymphoid tissue of the colon and the lower part of the small intestine. This extensive ulceration is common only with poorly nourished children such as are seen in asylum practice.

The leucocyte count is usually slightly increased (48, 200) but is of no diagnostic importance (103).

The physical findings are usually negative. The spleen is rarely palpable. Abdominal tenderness is sometimes present.

Occasionally bronchopneumonia, pyelitis (271), otitis media ulcerative stomatitis (447) and acidosis of the acetone body type (272) may complicate the course of bacillary dysentery in children.

As a general rule the appetite returns when the fever disappears but occasionally there may be persistent refusal to take food so that gavage is necessary for days and even weeks. Three months after recovery from bacillary dysentery, most children have regained their weight. Very few cases become chronic except in asylum practice. Death within the first three weeks or complete recovery is the usual course.

Diagnosis of dysentery in children (summary)

It would seem that in countries where amebic dysentery is not endemic (amebic dysentery is rare among children in the United States (273)), a presumptive diagnosis of bacillary dysentery can safely be made in children who have had a sudden febrile onset and are passing bloody stools. However, as in adults, the laboratory findings are the only absolute criteria. The bacteriological diagnosis of dysentery in children is much simpler than in adults for the intestinal reaction to dysentery bacilli is much more severe in the former and consequently the children's stools consist almost entirely of blood and mucus so that B. dysenteriae is quite readily isolated. In adults the presence of much fecal matter increases the number of B. coli in stool cultures to such an extent that B. dysenteriae is frequently overlooked.

Fifty to sixty per cent of the cultures of stools of children with dysentery are positive for B. dysenteriae, while in adults the percentage of positive stool cultures ranges from twenty-five to forty. Higher percentages may be obtained if several successive stool cultures are made. *The agglutination reaction of the patient's serum* is the simplest method of laboratory diagnosis and is even more satisfactory than in adults for non-specific agglutinins are rare in the serum of a child even at the low dilution of 1:20; there is less likelihood of the child having had a previous dysenteric infection, from which agglutinins might persist and confuse the diagnosis; the agglutination reaction is frequently positive earlier in the disease in children than it is in adults (occasionally the test may be positive on the second day.)

VIII. PROGNOSIS IN ADULTS AND CHILDREN

In epidemic outbreaks, whether in an institution or in a household, and in infants under one year and in adults over fifty years, the disease is likely to be especially severe, while in the very acute choleraic cases the mortality is also high. With these exceptions, in the great majority of bacillary dysentery cases coming under early observation, especially in Flexner infections, the ultimate *prognosis* is good although convalescence may be tardy. It is far otherwise with neglected patients who have suffered from dysentery from one to several months, often without any treatment, so that extensive ulceration of much of the large bowel is already present on their admission to the hospital. Albu (260) regards complete and permanent recovery from bacillary dysentery as an extremely rare event. Schmidt (402) and Strasburger (409) reported that 5 per cent of their cases of dysentery became chronic. This is a higher percentage than is usually noted. Schmidt stated that the mortality was 40 to 50 per cent among chronic as against 2 per cent in acute cases. In short, chronic bacillary dysentery is a much more difficult disease to deal with satisfactorily (3). The prognosis is poor in mixed infections with B. typhosus and B. dysenteriae especially when typhoid fever is the preceding infection (262). Job and Hirtzmann (369) state that malaria and bacillary dysentery are frequently associated. Owing to the injurious effects of malaria upon the intestines, convalescence from dysentery is apt to be prolonged in malarial subjects.

Mortality

The *mortality* among adults appears to have diminished during the past two centuries. In one epidemic in Holland in 1729 five thousand people died. The death rate at present varies considerably. Shiga (77) found for the whole of Japan that it was from 22 to 26 per cent. According to Kruse (34) the mortality in Germany is 10 per cent. In a small recent outbreak of Shiga dysentery in Dublin (356) the mortality was about 10 per cent. In Russia (78) and in the British Solomon Islands (404) it ranges from 9 to 18 per cent. Manson (79) reported the mortality from bacillary dysentery among Europeans in India to be from 3 to 22 per cent and among natives from 36 to 40 per cent. At El Tor (80) among the Mecca pilgrims the mortality was 64.4 per cent in 1909. Recent observations by Hotzen (359) in Germany have shown that the dysentery cases in the hot summer of 1917 amounted to 69 per cent of all the cases of acute disturbance of nutrition in infants. Of 123 patients in whom the diagnosis of dysentery was established bacteriologically, 44 per cent succumbed, and, even if only those cases be considered in which diseases other than dysentery could be excluded, the mortality was still 23 per cent. In a series of dysentery cases in American children (48) there were 67 white children with 14 deaths and 4 colored with 1 death, a total mortality of 21 per cent. All of the deaths were in children under 15 months of age. Among 114 cases treated at the Harriet Lane Home for Invalid Children from 1912 to 1918 inclusive, there were 33 deaths, a mortality of 29 per cent.

The reduction of the mortality among troops is very striking. At the siege of Dundalk, Ireland, in 1689 (6), 6000 men among 10,000 dysentery patients died, while in the Great War in spite of many cases there were comparatively few deaths. A quarter of 1 per cent of Nolf's patients (Flexner infections) in the Belgian sector died (55). In a total of 5000 cases, 79 per cent of which were Shiga infections, among the allied troops in Macedonia in the summer of 1918, the mortality was 3.5 per cent (355). Among 1023 cases in three epidemics in German troops on the western front the mortality was 0.4 per cent (433). In one American area in France several hundred mild cases occurred with no deaths. In Salonika the mortality was 1 per cent (58).

Factors influencing mortality and morbidity

This reduction in mortality may be due to decreased virulence of the organisms, to the absence of famine with which former epidemics were so frequently associated or more probably to better dieting and nursing. With the exception of serum therapy in Shiga infections, the medicinal treatment of dysentery is not sufficiently improved to account for the difference in mortality unless it be that it is now less meddlesome.

Shiga (46) states that the mortality among females is higher than among males. The incidence of bacillary dysentery is greatest among young men from twenty to thirty years of age and children under two years, perhaps because of more frequent exposure, for younger men are not as careful of the origin of their food and drink, while the milk diet of babies, which is an ideal medium for B. dysenteriae, is not as carefully handled as it should be. In infants under one year of age and adults over fifty years the mortality is higher. The majority of the deaths in the dysentery epidemic reported by Csernel (366) were in infants under two years of age and in adults over 70. In the epidemic at Barmen in 1899–1901 (359) the mortality among children was 6.3 per cent as compared with 4.6 per cent among adults. In the recent Dublin epidemic of Shiga dysentery (356) at ages up to forty-five years the mortality was 3.8 per cent and from 45 upwards 43.3 per cent. Kuntze (414) reported that the mortality in nurslings was 41 per cent as contrasted with 20.7 per cent in children over one and a half years. During the occasional epidemics of dysentery that still occur, the mortality is often low in the beginning of the epidemic season (May, June and July) and increases gradually, reaching the maximum in November and December. In winter the mortality is higher, due perhaps to the influence of the season and the chronic course of many of the cases. Rainfall has little influence on the prevalence of dysentery (4). Altitude, however, appears to influence the incidence of the disease. Other things being equal, dysentery decreases as the altitude increases (39).

All races are equally liable to dysentery. Individuals following indoor occupations are less liable to infection than agricultural laborers, soldiers, sailors and explorers (39). Dysentery is notably a poor man's

disease and a disease of enlisted men rather than of officers. Fatigue, hardship, exposure, starvation and restricted diet are frequently reported as predisposing factors of dysentery.

IX. TREATMENT

There are three fundamental principles in the treatment of bacillary dysentery in adults and children. *First*, to maintain the patient's nutrition and general condition by rest, nursing, diet and the relief of pain so that he may survive long enough to allow his immunity to rise and conquer the disease; *second*, to combat the effects of the disease in the patient by replacing the loss of body with saline; *third*, to kill the causative organism and to neutralize its toxins with specific sera and antitoxins. In addition to these three cardinal procedures, numerous drugs have been recommended to increase the elimination of intestinal contents.

Rest and diet

As soon as a presumptive diagnosis of dysentery has been made, the patient should be sent to bed and kept as quiet as possible. He should not be permitted to get up until the stools are practically normal and the fever has subsided. Rest in bed alone has a marked beneficial influence. Every effort should be made to keep the patient comfortable and free from pain. Morphine, hypodermatically has proven useful if the patient, either adult or child, becomes exhausted from frequent straining and the consequent loss of sleep. Paregoric, however, is the usual preparation of opium given to children. Bismuth has been recommended as a means of coating the inflamed mucosa and relieving griping and tenesmus. It usually fails, however. Bismuth, as roentgenology has proven (277), does not adhere to gastric or duodenal ulcers and leaves filling defects over tuberculous ulcers of the colon (278), so why should it be assumed to cling to dysenteric ulcers? Bismuth subnitrate should never be used for it may produce the serious features of nitrite poisoning. The subcarbonate is harmless. Hot water bottles on the abdomen frequently relieve pain. Application to the anus of ointment containing 4 per cent tannic acid or 5 per cent cocaine or the use of cocaine suppositories has been recommended (276). *Enemata* of warm

normal saline, starch solution or 4 per cent sodium bicarbonate at the outset have proven useful, especially in children. They not only clean the lower colon but also give the patient relief by reducing the tenesmus.

It is advisable to stop all food and to supply water as long as vomiting persists. Water must be given freely and offered as often as every hour through the febrile stages of the disease (279). Saccharine (1 grain to the quart) may be used for children who persistently refuse plain water. After the first twenty-four or forty-eight hours of the illness, vomiting usually ceases to be a prominent symptom. For *children* under two years, protein milk has been one of the best, if not the best food. This may be given in small amounts even in the first twenty-four hours; 1 ounce every four hours for the first day and then if this is well taken and vomiting does not interfere, it may be increased in amount up to 6 to 7 ounces every four hours according to the age and weight of the child. This food is offered whether or not the patient refuses it. As soon as the diarrhea abates and the child shows definite signs of improvement some carbohydrate may be cautiously added to the protein milk in small amounts (usually by the fourteenth day). In case a child is breast fed, this feeding should be continued but it is usually advisable to give alternate feedings of buttermilk or protein milk, as breast milk alone is too laxative in almost all instances.

The claim that a diet of lactose is beneficial in dysentery is not proved. It has been recommended partly because B. dysenteriae does not ferment lactose and also because a high carbohydrate diet changes the stool flora (171, 172, 173, 337). However, the ingested lactose is broken down into galactose and dextrose long before it reaches the distal third of the ileum and the colon where the dysentery bacilli are harbored. B. dysenteriae will readily ferment dextrose. Whether or not the stool flora is sufficiently changed by a high carbohydrate diet and whether these changes have any marked beneficial effect (171, 172, 173, 321) on the condition of the patient is not at all clear (163).

In older children and adults a milk diet (280) supplemented by broth, eggs and vegetable purees is probably the best.

The main consideration, as in typhoid fever, is to give as much non-irritating food as possible without producing nausea and diarrhea. The lack of appetite makes feeding extremely difficult and emaciation is frequent. In *children* this anorexia may be so pronounced as to cause death from inanition. It is advisable to wait until the temperature falls to normal before commencing forced feeding. Changing the diet from protein milk to buttermilk or even sweetened whole milk formulae does not appear to influence this lack of appetite. If a child refuses one type of food he usually refuses all food. If the desire for food does not return within one week, however, and the patient becomes very weak from inanition 2 to 6 ounces of water may be given by stomach tube every four hours for the first twenty-four hours. If vomiting does not result, one ounce of protein milk or breast milk is substituted for one ounce of water and the child is gavaged with the mixture. The strength of the mixture is increased, unless the patient vomits, until undiluted protein milk is given. Usually the child will regain his desire for milk given by bottle or cup after a week of gavage feeding. Picard (352) recommends the value of cocoa as a food for children with dysentery.

Injections of normal salt solution

In the more severe cases when the loss of water by the bowel has been extreme and when the patients are markedly dehydrated and cannot retain fluid given by mouth or rectum, sterile normal saline or 5 per cent dextrose should be given *intravenously* in amounts of 125 to 500 cc. according to the size of the patient. Instead of normal saline Von Jaksch (339) recommends the injection of a solution containing sodium chloride 15 parts, calcium chloride 0.45 parts and potassium chloride 0.7 parts in a liter of water. Weinberg, Singer and others (339) inject hypertonic saline. In small children the saline or 5 per cent dextrose may be administered *intraperitoneally* (281). Normal saline is preferable as it is more readily absorbed. This procedure has undoubtedly saved many lives. In many cases repeated injection of saline or dextrose either at twelve or twenty-four hour intervals may be necessary to replace the great loss of body fluid. Subcutaneous injections are painful and do not allow the administration of sufficient fluid. They may be used, however, in children

if the abdomen is distended. Fluid administered by rectum either by syringe or by a Murphy continuous drip is seldom retained or absorbed by children. However, fluid, either saline, 5 per cent dextrose or boiled tap water, may be given from a continuous drip apparatus into the stomach by a nasal tube fastened in place by adhesive. Stewart (434) has found that in children a drip delivering fifteen drops per minute may be continued four to five days without producing nausea. It may be given continuously or in periods of a half hour alternating with equal periods of rest. In this way 500 to 1000 cc. of fluid may be given daily. If the infant has persistently refused his feedings, protein milk may also be administered through the nasal tube by disconnecting the drip apparatus and substituting a funnel. The prolonged use of a nasal drip is not without danger, however, for fatal erosions of the oesophagus and stomach have occasionally occurred (451).

Specific serum therapy

As B. dysenteriae (Shiga) and (Flexner) are absolutely different culturally and serologically, the success of the serum treatment of bacillary dysentery will depend upon an accurate knowledge of the type of the causative organism in each case and the use of serum containing antibodies for that variety. Polyvalent sera (57, 121, 282, 283, 381) containing antibodies for both Shiga and Flexner varieties are, of course, obtainable and should be used in severe cases until stool cultures or the agglutination reactions of the patient's serum have revealed the type of the infection. However, as the results in Shiga infections have been more favorable than those in Flexner infections, they will be discussed separately.

The therapeutic sera are prepared by the immunization of horses with cultures of Flexner and Shiga bacilli or with the toxins of the Shiga organism. Flexner and Amoss (283) have reported a rapid method for the production of potent antidysenteric serum. Agglutination tests with the dysentery bacillus isolated from the patient's stool and the available therapeutic serum (unless Shiga antitoxin is used) should be made whenever practical (57) to determine whether there are antibodies for this particular strain. Otherwise, serum therapy is often useless. Attempts are now being made (284) to

standardize Shiga toxins and antitoxins in much the same way as those of the diphtheria bacillus.

a. In Shiga infections

A potent antidysenteric serum should contain antibodies against the exotoxin as well as the endotoxin. Such sera and antitoxins are now obtainable (119, 283). Antitoxin (made by immunizing horses with toxins) is preferable in the treatment of Shiga infections but sera made by the injections of the organisms themselves are also efficacious. Olitsky and Kligler (119) found that a polyvalent antidysenteric serum, although prepared by injecting the cultures alone, contained at least 2000 anti-exotoxic units per cubic centimeter as well as anti-endotoxin and other antibacterial bodies.

Shiga (46) in the Institute for the Research of Infectious Diseases in Tokio has formulated the following rules for the administration of antidysenteric serum or Shiga antitoxin:

1. In mild cases the serum is injected once in a dose of 10 cc.
2. In cases of medium severity the serum is twice injected in doses of 10 cc. The interval is from six to ten hours.
3. In severe cases the largest amounts are injected (40 to 60 cc.) but the daily dose does not exceed 20 cc.

This dosage is very conservative. I have used twice this amount subcutaneously and intramuscularly in children without reactions (285). The doses for adults could be trebled advantageously. The best method of injection is intravenously, care being taken to introduce the serum slowly and to avoid shock. Should a patient give a history of having had asthma, or of being sensitive to horse serum or of having had previous serum treatments, one drop of sterile diluted horse serum (diluted 1:10 with normal saline) should be injected intradermally (401). If the patient has a local or general reaction to this within one hour, 1 cc. of serum should be injected subcutaneously for desensitization. Six to eight hours later the full dose of serum may be given slowly, either subcutaneously or intravenously. If the patient fails to react to the intradermal serum test within one hour, the full dose may be injected at once.

For adults many authorities (286, 287) advise the intravenous injection of 60 to 100 cc. of polyvalent serum as early as possible

after admission, followed by 40 to 80 cc. subcutaneously or intramuscularly within 12 hours in severe cases. Shiga antitoxin or Flexner serum should be used as soon as the type of infection is known. In children, however, the reactions to intravenous serum are often so severe that injections should be subcutaneous or intramuscular. Serum sickness with fever, urticaria and arthralgia frequently follows serum therapy on about the tenth day (55) both in adults and children but is rarely alarming.

Lantin (288) reports that serum given by rectum is efficacious. If Besredka's (230) theory that the intestinal lesions are due to the contact of dysentery endotoxin with the intestinal mucosa is correct, the administration of antitoxin or antiserum by mouth or rectum in large doses is the most logical method, for it is in the intestine that the endotoxin must be neutralized. Serum given intravenously or subcutaneously must first be excreted into the intestine to counteract the effect of the endotoxin on the intestinal mucosa. Intravenous or subcutaneous serum therapy then in dysentery might be compared to similar procedures in the serum treatment of cerebrospinal meningitis for the administration of specific serum intraspinously in meningitis is obviously the more direct and efficacious method. It may be found that the direct administration of antidysenteric serum by duodenal tube, as Smith (289) suggests, or by rectum (288) or even by appendicostomy or colostomy wounds will reduce the mortality in dysentery more than by the intravenous and subcutaneous routes. Perhaps the efficacy of intravenous and subcutaneous serum therapy in Shiga infections and the apparent lack of benefit from this procedure in Flexner infections may be due to the fact that the Shiga bacillus produces part of its effect by the action on the central nervous system of absorbed circulating exotoxin while the whole picture in Flexner infections is the local action of the endotoxin on the intestinal mucosa.

Under serum therapy in Shiga infections in adults, the disease in its first stages according to Shiga (46) and Flexner (381) is quickly cured or the symptoms markedly ameliorated. In one or two days after the injection, the blood and mucus usually disappear from the stools, pain and tenesmus cease and the patient seems entirely well. On the later use of the serum (at the end of the first week) improve-

ment of all symptoms is usually noted after a few days. Recovery usually occurs after a week. The effect of the serum upon the fever is very striking; in the majority of cases the temperature may be lowered to normal or even below normal on the next morning after injection. In the ulcerative stage, the action of the serum is not so pronounced as in the earlier stages; nevertheless healing of the ulcers with cicatrization often takes place. Even in the later stages the results are far better than those by any other method of treatment. The mortality in Shiga infections in adults under the use of serum is usually reduced by one-half (54, 78, 117, 243, 290, 291, 292, 390) (from 22 to 26 per cent under medicinal treatment to 9 to 12 per cent (46)). Shiga antitoxin has also been very successful in reducing mortality (78, 118) in adults. In children with Shiga infections, serum and antitoxin, in my limited experience (285), has been rather disappointing. This may perhaps be due to the fact that children often do not respond as well as adults to large subcutaneous and intramuscular injections of horse serum.

b. In Flexner infections

Treatment of Flexner infections with bactericidal and agglutinating sera has been attempted in many epidemics. The therapeutic effects are not nearly as striking as those in Shiga infections and in fact are rather disappointing both in adults (55, 253, 390) and children (138, 200, 285, 293). With large intravenous doses of 40 to 100 cc. of anti-Flexner or polyvalent serum in Flexner infections some authors have noted a reduction in mortality (54, 64, 80 286, 287, 291, 381) but equal benefit is frequently noted with the same amounts of horse serum (73) or normal saline injected intravenously or intraperitoneally. In a few cases of Flexner infection in children which I have treated or seen treated with anti-Flexner serum there has been little or no beneficial result (285). Perhaps the administration of anti-Flexner or polyvalent antidysenteric serum by mouth, duodenal tube or rectum so that it will reach the intestine directly may be of benefit.

Vaccine therapy

Following Shiga's (46) work with vaccines as a prophylactic measure in dysentery epidemics, other observers (55, 253, 310, 311, 405, 415)

have reported benefit from similar procedures in the treatment of the disease. On the other hand, Rogers and others (312) have had disappointing results with vaccine therapy. As no well controlled experiments have been reported with this method, it is reasonable to suppose that the benefit is more apparent than real as Whittington (313) has proved for the vaccine treatment of typhoid fever. In the treatment of carriers of B. dysenteriae, vaccines have apparently been more successful (7, 55, 175).

Proteosotherapy

Nolf (55, 309) and others (104) have advocated intravenous and subcutaneous injections of 1 per cent Witte's peptone as a valuable therapeutic measure in dysentery. The resulting peptone shock is however occasionally alarming and the dose of the peptone solution must be accurately graded. The injection should be made very carefully and slowly. As a matter of fact, the majority of Nolf's cases were Flexner infections (55) and inasmuch as the mortality with this type is extraordinarily low, "proteosotherapy" should await more confirmation before being widely used.

Drug therapy

Bleeding, purgation, ipecacuanha and occasionally opium were the armamentarium of the past century and a half (10, 11, 12, 25, 30, 52, 294). The first procedure has fallen into disrepute and purgation and ipecac will probably follow. Morphine (420) and paregoric, as has been stated previously, are probably the only drugs at all useful in the treatment of bacillary dysentery.

Cathartics have little to recommend them. Purgation cannot assist the rapidly moving intestine to evacuate its contents and the mucosa has already had sufficient irritation. That castor oil, sodium or magnesium sulphate (295) and calomel (271) at the onset are of value would seem improbable for the infection itself will increase the number of bowel movements before these drugs will have time to produce catharsis. If cathartics and frequent evacuations could rid the intestine of the offending bacteria, all dysentery cases would be of short duration.

Ipecacuanha (39) has been highly rated as efficacious in the treatment of bacillary dysentery. That it and its active principle emetine are practically specific for amebic dysentery there is no doubt, but the majority of observers deny its benefit in the bacillary variety. In fact many physicians in practice away from laboratories make a diagnosis of bacillary dysentery if ipecac and emetine fail to cause improvement within a few days. One patient with bacillary dysentery treated with benzyl benzoate (372) was apparently benefited. Kohler (412) recommends a German drug mixture called "antidysten." One observer (296) advocates the use of belladonna to counteract the excessive activity of the thyroid and suprarenal glands in dysentery, while another (297) prescribes adrenalin by mouth and rectum to quiet tenesmus. Inasmuch as suprarenal insufficiency has been reported (65) as a complication of dysentery, the adrenalin is perhaps the more logical of these drugs but it is doubtful whether either is really useful.

The ingestion of 300 grams of *kaolin* or *animal charcoal* in oatmeal is advocated as a means of adsorbing dysentery organisms and also rendering the stools more solid (270, 314). Hirsch (315) states that rectal injections of kaolin are more efficacious than the administration by mouth. Weise (316) on the other hand, advises against the use of kaolin on the ground that it forms irritating lumps and does more harm than good. In young children with watery non-dysenteric diarrhea I have found that kaolin and animal charcoal in daily doses of 10 to 20 grams administered in milk will reduce somewhat the number of stools and render them solid by their mechanical action of adsorbing fluid but their beneficial effect has not been particularly apparent.

Irrigation of the colon

In the later stages of the disease and especially in chronic cases, rectal irrigations with tap water (298), 0.01 per cent silver nitrate (79, 299, 300), 0.25 per cent tannin, 0.01 per cent methylene blue (301), permanganate (3), 2.0 per cent sodium salicylate (302) and other solutions (303) have been recommended but their benefit is not striking. Ohly (353) found a 10 per cent ichthyol salve or a 2 per cent silver salt salve useful for local treatment, followed by

astringents. Schiff (304) reported that rectal injections of 300 cc. of 1 per cent formalin twice a day and continued until the stools were more consistent and then once a day for the next week, were beneficial in Shiga infections. This mode of therapy is painful however. The pain due to repeated introductions of a rectal tube may be largely obviated by the preliminary use of cocaine suppositories, but injections in many cases are not tolerated or retained. In obstinate cases irrigations and flushing of the colon with these solutions through a *colostomy* or *appendicostomy* wound have also been advocated (7, 305, 421) but have not met with enthusiasm (390). Allowing the intestinal contents to drain through a caecostomy wound and thus reducing the irritation of the mucosa of the large intestine has been reported as advantageous (336).

Cooke (306) and others (307) advise touching all chronic ulcers that can be reached through a proctoscope with a solution containing 60 to 120 grains of silver nitrate to the ounce until tenesmus is relieved. The use of sigmoidoscope, however, is occasionally dangerous (446). According to Rogers (3) copper sulphate in a strength of 1 grain to the ounce similarly used is also often of great value and has the advantage of being less painful than silver nitrate. The same author (308) has shown experimentally that silver nitrate in a dilution of 1:10,000, would kill B. dysenteriae in five minutes.

X. MEANS OF SPREAD (EPIDEMIOLOGY)

That dysentery is a communicable disease has been shown, by the review of the numerous epidemics that have occurred among the civilian population and among troops. No one exclusive method of spread or conveyance has been proved but it is probable that, as in typhoid fever, the Oslerian triad (317) of fingers, food and flies is the most important factor.

Graham Smith (318) and others (319, 356, 358, 368, 382, 383) have shown that flies are capable of spreading dysentery. The curves of the case incidence of dysentery among the British troops in Salonika (57) in the A. E. F. (67) and in our series of cases in children (48) demonstrated that the greatest incidence occurred during the summer and autumn months in which flies were the most numerous. B. dysenteriae was isolated from the feet of flies caught in one of the

Salonika hospitals. After contact with food infected with dysentery bacilli flies could carry and disseminate these organisms for twenty-four hours (320). Bishopp and Laake (388) have reported that flies may frequently travel eight miles from the point of liberation in less than a single day. Paraf (358) made the following observations in a hospital containing patients with bacillary dysentery where flies were very prevalent: (1) Flies swarming round the dejecta of dysentery patients were frequently found to be carriers of the Shiga bacillus. (2) The Shiga bacillus was found in the bodies of flies caught in wards in which dysentery had occurred. (3) The dysentery bacillus was found in food exposed to the air in surgical wards in which there were swarms of flies. (4) As regards the mode of transmission, cultures of flies' legs and wings were positive in only two out of sixteen cases, whereas cultures of the alimentary canal were positive in eleven out of twenty-four cases. (5) The maximum duration of the survival of the dysentery bacillus in the fly's intestine was found to be five days. After that time the cultures were negative.

Through the winter and early spring there are comparatively few cases and in some parts of the country the disease disappears altogether to reappear the next summer. During the flyless months the infecting of food by fingers that have handled the excreta of dysentery patients and contact infections from contaminated clothing and utensils are logical explanations of the spread of dysentery (335). Direct ascending infections from the use of infected latrines (236) and syringes may possibly occur but are surely not frequent. The infection in these cases is probably not ascending but more likely due to the soiling of the fingers.

Carriers of dysentery bacilli have frequently been reported (47, 73, 75, 117, 151, 175, 186, 187, 214, 239, 335, 213). Convalescents may harbor the organisms for many months (46). It is probably by means of these carriers and convalescents that dysentery is carried over from one epidemic season to the other and from one locality to another. Lentz (110) reported the experience with a soldier who, after recovery from dysentery, left his regiment and was the source of a dysentery epidemic in his native village. Other widespread epidemics have similarly been traced to individuals who were convalescent or supposedly cured of dysentery (29, 176, 357, 366).

Direct contact with a neighbor's child suffering from dysentery or with an adult with a mild diarrhea are responsible for many cases of dysentery in children (48). Two cases of dysentery in newly born infants whose mothers had dysentery have been reported (417). Two or more cases frequently occur in the same house. Small hospital epidemics are not uncommon. The institution of special wards for and the strictest isolation of dysentery patients usually reduces the incidence of infections acquired in hospitals.

Water-born epidemics of dysentery are sometimes reported (57, 322). Dysentery bacilli have occasionally been isolated from the suspected rivers or wells (46) and it has been shown experimentally (176, 322) that these organisms can survive nine days or more in samples of the water (57). Shiga (46) reported one outbreak due to bathing in a stream. It was found that an epidemic of dysentery existed in a village higher up the river and the water had been contaminated by the washing of the infected clothes. Another epidemic in Japan was traceable to the use of a common bath house. An epidemic in Metz in 1870 was restricted to two regiments who derived their water supply from fecally polluted wells (323). The substitution of distilled water in the British Navy (324) and of artesian well water among the Dutch troops in Java reduced the incidence of dysentery nearly to a tenth. Kligler (448) has shown that soil pollution by dysentery is very limited. It probably plays little or no rôle in the spread of the disease.

Amebic dysentery, however, is more likely to be spread by drinking or bathing in infected water while flies are probably the more common method of dissemination of bacillary dysentery during wars (57, 319, 322).

In my experience the infection of the milk and food in the individual households or army messes by flies or attendants' fingers is the probable explanation of its spread. Lorenz (375) in an epidemic of dysentery in an orphanage reported that the milk was probably infected after sterilization by one of the servants who suffered from a dysentery-like condition.

The institution of Baby Welfare Clinics and Feeding Stations in several cities has probably been a great factor in the reduction of dysentery in children, for in the past few years since these have been

established the number of cases of dysentery in children admitted to hospitals has become steadily smaller. Mothers are taught to keep their infants clean and to give them clean food. Occasionally in epidemics of dysentery among children the milk supply has been suspected (139). I was unable to trace any relationship between any of my cases (48) and the source of the milk supply. The pasteurization of milk and its distribution in bottles instead of being sold in bulk at corner grocery stores have had an important influence in reducing dysentery. This has probably not been because dysentery bacilli in the original milk have been killed by pasteurization, for B. dysenteriae has rarely, if ever, been found in a milk supply, but because the use of pasteurized and bottled milk has educated the public to the necessity of the careful handling of this readily infected food. Knox and Powers (325) were able to reduce the incidence of dysentery among the children whose feedings were supervised by the Babies Milk Fund Association of Baltimore, by insisting that the infants be fed only milk mixtures that have been boiled directly in the feeding bottles (so that the possibility of contaminating the boiled mixture by transferring it to the bottle is obviated). Dysentery is rare in breast fed children (152).

XI. PROPHYLAXIS

When cases occur or are suspected either among adults or children, the patient should be promptly isolated. Those engaged in caring for patients with dysentery should not prepare food for other individuals. The breast feeding of infants should be encouraged. When this is impossible the milk mixtures and the bottles or containers should be boiled. Flies should be suppressed and food and feces rigidly separated. Excreta from patients and all open latrines must be adequately covered or disinfected with lysol, carbolic or other antiseptics. Before a patient is discharged as cured and released from quarantine he should have three negative stool cultures (69) over a period of two weeks. Inasmuch as it is sometimes impossible to detain for long periods ex-soldiers who have chronic dysentery or who are carriers of dysentery bacilli, the British (386) notify the local health officer of the man's home town before discharging any of these patients so that he may enforce precautions. Only by the

rigid application of these measures can the spread of dysentery be prevented.

The first great step toward the reduction of the incidence of bacillary dysentery in children will be made as soon as it is more generally recognized that the great majority of cases of bloody diarrhea in children are true dysentery. The second step will consist in making this disease both in adults and children reportable to the Health Authorities so that the same measures that have made typhoid fever a comparatively rare disease can be instituted against bacillary dysentery.

Prophylactic vaccination

Inoculation with dysentery vaccines may prove as valuable as is the prophylaxis of typhoid fever particularly for children in cities in which dysentery is prevalent. Heretofore, however, the severe reactions to these vacines have made their general use impractical (222, 230, 326, 327). The immunity conferred probably lasts two to three months (222). Vaccines of the Shiga bacillus are very toxic and frequently give rise to sterile abscesses at the point of inoculation. To avoid this Shiga (46, 241) first used simultaneous injections of vaccine and serum. Various methods of reducing the toxicity of Shiga vaccines have been advocated (328, 366). Busson (329) recommends prophylactic inoculations with dysentery toxin-antitoxin mixtures. Graeme Gibson (330) was able to eliminate the reaction to dysentery vaccine and still establish protection by the injection of a saline suspension of B. dysenteriae (Shiga) and (Flexner) mixed with an equal quantity of absorbed polyvalent antidysenteric serum. The results of this technique are encouraging and further experience may establish its usefulness.

Vincent (349) using an ether killed polyvalent antidysenteric vaccine, containing five Shiga and seven Flexner strains, in doses of 500,000,000 to 750,000,000 bacilli in a series of 2175 men found that during a severe epidemic the incidence of infection was twelve times greater among unvaccinated individuals than among his vaccinated series. The reactions to the injections were very slight. Spolverini (351) recently stated that in a small series of children a vaccine made with various strains of B. coli was useful as a means of curing and preventing enterocolitis.

Whether or not Besredka's (230) method of administering prophylactic vaccines by mouth will prove effectual in man remains to be seen.

Dysbakta (Boehncke) a German proprietary vaccine (probably a combination of dysentery bacilli, toxin and antitoxin) in spite of earlier favorable reports (328, 331) has recently been shown (332) to have nothing to recommend it. *Lipovaccines* made according to Le Moignac's (333) method have been advocated (334) because of their mild reaction, but the difficulty of insuring their sterility has detracted from their value.

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CYANOSIS

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INTRODUCTION

Cyanosis (from the Greek κύανος, meaning dark blue) indicates, as is well known, a blue or bluish color of the skin, of the mucous membranes, and of other organs, the retina, spleen, liver, kidneys, etc., usually not visible. To its presence or absence importance has been attributed in the differential diagnosis, the functional diagnosis, and the prognosis of various diseases. Since cyanosis through bedside observation was clearly recognized as a definite pathological phenomenon and in the middle of the eighteenth century through combination of clinical observations and morbid anatomy was ascribed to various pathological anatomic disturbances, it has been explained in many different ways. It has been ascribed to admixture of venous and arterial blood, to stasis in the systemic circulation, to polycythemia, and to overloading of the blood with carbon dioxide. It has figured as a disease in itself (morbus cæruleus)[1] and as a symptom of other diseases. Special therapeutic procedures (oxygen inhalation, venesection) have often been used against it.

DEGREE, DISTRIBUTION, AND SHADE OF CYANOTIC COLOR

The coloration of cyanosis is diffuse like the coloration of anemia and icterus. It may be generalized, but is usually more marked in some regions than in others. In most cases, however, the cyanotic color is found only in certain regions; lips, nose, cheeks, ears, hands, and feet. The intensity of cyanosis may vary from a just perceptible blue color to almost black. Similarly, the shade of the color may differ as indicated by the original names used to describe it. It has been called ictère bleue, ictère violet, mélasictère, maladie bleue,

[1] "La cyanose est une maladie constituée par l'introduction du sang veineux dans le système artériel général, en vertu de communications ouvertes, soit entre les cavités droites et gauches du cœur, soit entre les principaux troncs vasculaires: maladie qui est accompagnée de la coloration bleuâtre, livide, de la peau et des membranes muqueuses" (Gintrac, 1824, p. 7).

and cyanopathie, before Baumes introduced the present name in 1801. More recent writers have used the terms leaden blue, cherry-red-blue (Stadie, a), heliotrope, or lilac (Abrahams, Hallows, and French). The heliotrope color has thus far been observed only in connection with severe lung involvement, particularly in influenzal pneumonia. It is in many cases not easy to decide whether or not a cyanotic skin color is present, and it is also difficult to compare the intensity of cyanosis in different cases or in different regions. An oxyhemoglobinometer by means of which the intensity or shade of the cyanotic color could be matched has recently been devised by Flagg. It consists of a color wheel by means of which varying percentages of light and dark red can be mixed. So far the method has not been applied to cases other than patients with cyanosis resulting from anesthesia.

CAUSE OF CYANOTIC COLOR

As in anemia, the essential cause of the coloration of cyanosis is a change in the character of the circulating blood. In this respect it differs from icterus, the causative factors of which are present not only in the blood but also in the intervascular tissues. For this reason the icteric color is often most pronounced in the sclera, where the capillaries are very few and united at intervals so wide that a diffuse cyanotic color can hardly be produced. For the same reason cyanosis, unlike icterus, disappears when the blood is pressed out of the skin.

The blood component responsible for the production of the cyanotic color is that portion of the hemoglobin which is not in the state of oxyhemoglobin, but is either normal reduced hemoglobin, or methemoglobin, or sulfhemoglobin.[2] In this paper we are considering

[2] The autotoxic enterogenous type of cyanosis was the name given by Stokvis (1902) to a condition of cyanosis in a patient suffering from enteritis. Stokvis could demonstrate spectroscopically the presence of methemoglobin in the blood. Similar observations were at the same time published by Talma. Stokvis and Talma ascribed the occurence of cyanosis to the presence of methemoglobin. Cf. cyanosis in cholera morbus.

However, it is clear that the mere qualitative demonstration of methemoglobin or sulfhemoglobin in the blood of such patients even if it is very suggestive, is not sufficient to exclude other causes. The same applies to Hijmans van den Bergh's conclusions. Quantitative determinations, not only of the methemoglobin and sulfhemoglobin, but also of the amount of ordinarily reduced hemoglobin, are, therefore, required before any definite conclusions can be drawn.

cyanosis due only to increased oxygen unsaturation of the blood, i.e., to an increased amount of reduced hemoglobin.[3] The amount of reduced hemoglobin, or the volume per cent of oxygen unsaturation of the blood,[4] must reach a certain value before cyanosis appears. This is in part, of course, due to the fact that a certain proportion of blue must be mixed with the red in order to change appreciably the blood color, but it appears to be due chiefly to the opacity of the epidermis, by reason of which, a certain intensity of blue color is required in the corium in order to show through. *For this reason cyanosis appears to be chiefly dependent on the absolute concentration of reduced hemoglobin in the blood, rather than on the ratio of reduced to oxygenated* (Lundsgaard, 1919). About 5 grams of reduced hemoglobin per 100 c.c. of capillary blood appear necessary to cause cyanosis, the amount of oxygenated hemoglobin also present having relatively little effect. An anemic with less than 5 grams of hemoglobin per 100 c.c. of blood cannot usually become cyanotic.

It is the blood in the capillaries, and possibly in the arterioles and venules of the subpapillary plexus as well, which produces the cyanotic skin color. The arteries and most of the veins are so far away from the skin that their content cannot influence the skin color. A few veins, to be sure, are situated superficially enough to influence markedly the skin color, but they are too few and too far apart to cause any diffuse coloration. A blue color confined to the skin over the superficial veins is therefore not termed cyanosis.

The fact that the oxygen content of the blood changes during its passage through the capillaries, every section of which may influence

[3] Cyanosis should not be confused with anoxemia, which indicates a condition where there is, for some reason or other, an oxygen want in the tissue cells. Anoxemia may be present without cyanosis, and cyanosis may be present without the appearance of any anoxemic symptoms.

"The word 'anoxæmia' should evidently be taken as signifying a condition in which the *free* oxygen in the systemic capillary blood is abnormally diminished;" (Haldane, Respiration, p. 124).

[4] It is convenient to express reduced hemoglobin concentration in terms of oxygen unsaturation, since oxygen values are those experimentally determined. One cubic centimeter of oxygen combines with 0.75 gram of hemoglobin. So that 5 grams of reduced hemoglobin may be expressed as $\frac{5}{0.75} = 6.7$ volumes per cent of oxygen unsaturation. "Volumes per cent" expresses, as usual, cubic centimeters of a gas in 100 c. c. of a fluid.

the skin color, makes it difficult to find an exact quantitative expression for the threshold value of oxygen unsaturation causing cyanosis.[4] It cannot be expressed solely by the amount of oxygen unsaturation at the arterial ends of the capillaries, nor solely by the unsaturation at the venous ends. If the arterial unsaturation is A, and the venous V, the values for the capillary unsaturation, C, must change from A to V during the passage of the blood through the capillaries. The average of the successive sections of a capillary will give an unsaturation larger than A and smaller than V. Lundsgaard (c) has expressed the mean capillary unsaturation as $\frac{A+V}{2}$, that is, the mean between arterial and venous unsaturations. He found in a series of cases that cyanosis appeared when the mean capillary unsaturation $\frac{A+V}{2}$ approximated 6 to 7 volumes per cent, which corresponds to about 5 grams of reduced hemoglobin per 100 c.c. of blood. This he called the threshold value for the appearance of cyanosis.

MODIFYING FACTORS OF CYANOSIS

While oxygen unsaturation of the capillary blood is, it appears certain, the essential cause of cyanosis, there are modifying factors which affect the resulting coloration, and which probably vary the threshold concentration of reduced hemoglobin in the capillary blood necessary to produce visible cyanosis. Such factors may also considerably change the intensity of cyanosis caused by a given amount of oxygen unsaturation.

The principal factors appear to be (1) the thickness of the epidermis (which in itself has no vessels); (2) the normal or pathological pigment of the skin (in sunburnt people, in the black and yellow races, in patients suffering from icterus, from Addison's disease, from argyria, etc.); (3) normal and pathological variations in the color of the blood plasma (varying concentration of normal and abnormal pigments in the plasma, variations in lipoid content, etc.; here may also be included a possible effect of large increase in the leucocytes, as in leucemia); (4) variations in the concentration of oxidized hemoglobin in the blood; (5) variations in number, width, and length of blood-filled capillaries in a given surface area; (6)

variations in the extent to which the average capillary blood approximates in its unsaturation more nearly the arterial than the venous blood or vice versa. *These modifying factors cannot, however, produce cyanosis themselves; they can influence the amount of oxygen unsaturation necessary to give the skin a perceptible blue color, and can modify the shade of color produced.*

Not much information is at hand as to the influence on cyanosis of any of the above enumerated six factors, and certainly not any information which allows a quantitative discussion of the problem. The influence of the first two factors, the thickness of the epidermis and the skin pigment, is evident. They are partly responsible for variations in shade and intensity of cyanotic color in different regions of the body and in different individuals. Being fairly constant features over a long period of time, these factors cannot be responsible for transitory variations in cyanotic color in a given region. The third factor, the color of the plasma, does not vary from one region of the body surface to another, nor does it vary much over a short period of time. If this factor has any appreciable influence on the cyanotic color, it can cause only slight modifications in the color (probably most in the shade of the color) present in different individuals. The influence of the fourth factor, the concentration of oxyhemoglobin in the blood, is not easy to analyze. From observations of patients and from blood analyses in different individuals (Lundsgaard, c), in whom the hemoglobin concentration varied over a wide range (anemic and polycythemic patients), one cannot decide whether the degree of cyanosis varies in direct or in inverse proportion to the concentration of oxyhemoglobin. It appears that the influence of this factor is relatively smaller than one might expect.

The variations in number, width, and length of blood-filled capillaries per unit of skin (or surface) area, undoubtedly rank high in importance. Due to variations in these factors the same concentration of reduced hemoglobin in the capillaries may produce a cyanotic color of varying intensity in different individuals, in different skin regions of the same individual, and at different times. During the last few years our knowledge of the anatomy and physiology of the capillary system has increased considerably.

This is mainly due to two circumstances: first, to the method for direct microscopic examination in vivo of the skin capillaries

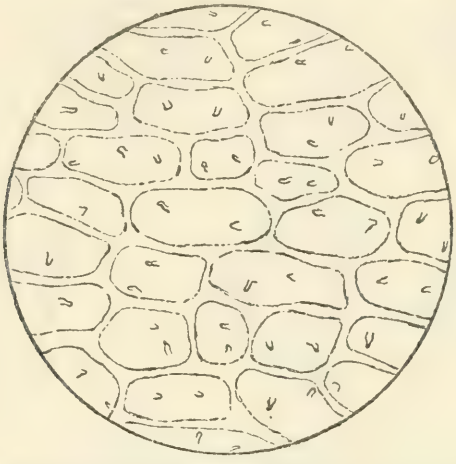

FIG. 1. CAPILLARIES FROM THE SKIN OF THE FIRST PHALANX OF THE FINGER NEAR THE METACARPOPHALANGEAL JOINT (AFTER WEISS AND HOLLAND)

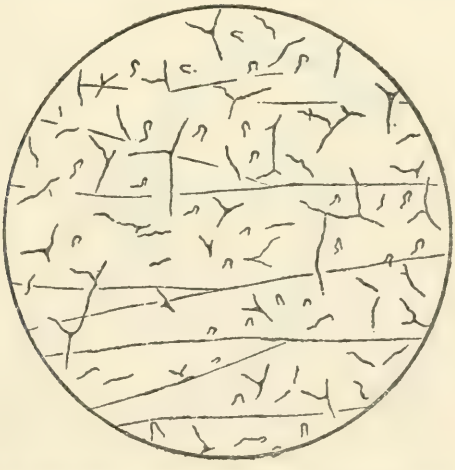

FIG. 2. CAPILLARIES FROM THE BACK OF THE HAND. A FEW DEEPER VENULES ARE SEEN (AFTER WEISS AND HOLLAND)

ingeniously devised by Lombard (1912) and Weiss (1916); second, to indirect (Dale and Richards) and direct (Krogh) proof of the existence of a capillary motor function independent of other parts of the

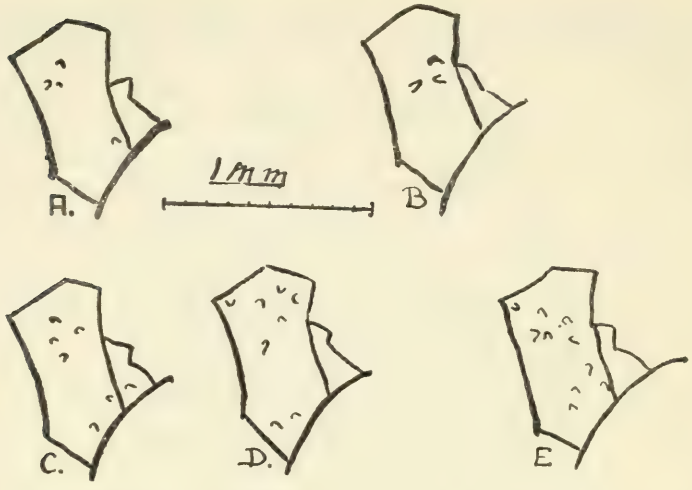

FIG. 3. THE DIAGRAMS A, B, C, D, AND E GIVE THE NUMBER OF OPEN CAPILLARIES IN THE SAME AREA FROM THE BACK OF THE HAND OBSERVED AT VARIOUS TIMES OVER A PERIOD OF 4 DAYS (AFTER CARRIER)

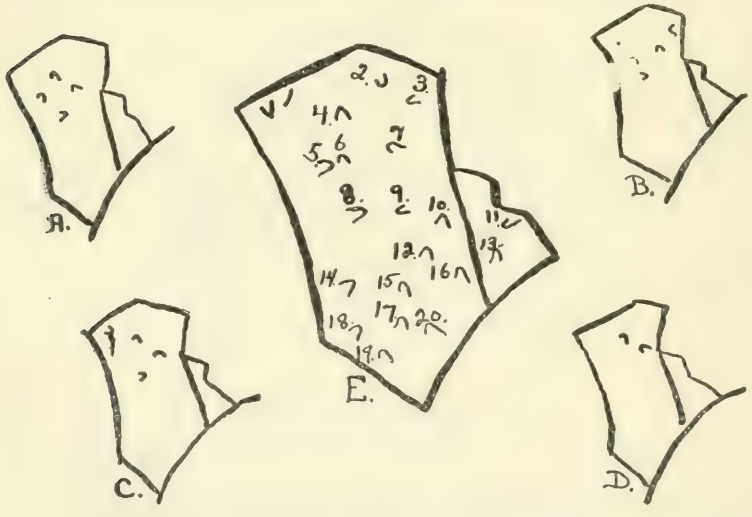

FIG. 4. DIAGRAMS A, B, C, D, AND E GIVE THE NUMBER OF OPEN CAPILLARIES IN THE SAME AREA AS IN FIG. 3 AT DIFFERENT OBSERVATIONS OVER A PERIOD OF 13 MINUTES. DIAGRAM E IS DRAWN TWICE THE SIZE OF THE OTHER FIGURES AND EACH CAPILLARY IS GIVEN A NUMBER. IN E ALL THE CAPILLARIES ARE OPEN AS A RESULT OF LIGHT PRESSURE (AFTER CARRIER)

vascular system. We shall briefly discuss a number of facts which are of importance to our problem even though their quantitative relationship to production of cyanosis cannot yet be worked out.

Variations in the number, width, and length of the skin capillaries in normal subjects under natural conditions. Weiss and Holland have given a detailed description and several illustrations of the variations in density of the capillary network in various regions of the skin. Figures 1 and 2 illustrate the difference in the capillaries in the skin over the first phalanx of the finger (fig. 1), and the back of the hand (fig. 2). At the last place a few deep venules are observed between the capillaries. Such variations are found, however, not only at different regions of the skin, but also in the same skin region at even very short intervals of time, as demonstrated by Carrier (figs. 3 and 4). This is due to the opening (term introduced by A. Krogh, 1919, b) of a varying number of capillaries by the independent capillary motor function. The observations on which figures 3 and 4 are based were made on the back of the hand. In the wall at the finger-nail the number of opened up capillaries is much more constant, indicating probably that nearly all the capillaries normally are open. (Carrier, p. 535.) However, great variations in number, shape, width, and length of the capillaries of the nail wall take place from one individual to another and from one finger to another, as shown by Rosenberger, Schur, Moog and Fhrmann, and Secher. Figures 5, 6, 7, and 8 are taken from Secher's publication and show this very clearly. The observations were made on individuals in whom one might expect normal conditions.

Variations in the number, width, and length of the capillaries in abnormal and in pathological conditions. To the above mentioned variations, found in normal or presumably normal subjects under normal conditions, may be added even larger but not yet well defined variations found, after application of stimuli to the skin, or in disease. Of particular interest for our problem is the effect of thermic stimuli, by means of which cyanosis, as is well known, can be produced. The morphological and functional changes which take place in the capillaries after thermic stimuli and give rise to varying skin colors (erythrosis, cyanosis) are described by Bruns and König and Carrier and will be considered more in detail in the chapter on

acrocyanosis. If stasis is applied to an arm, by means of von Recklinghausen's manchette for instance, it is easily demonstrated that not only does the number of blood-filled capillaries increase, but their

Fig. 5 Fig. 6

Fig. 7 Fig. 8

FIGS. 5 TO 8. CAPILLARIES AT THE WALL OF THE NAIL IN DIFFERENT INDIVIDUALS IN WHOM NO CHANGES IN THE CAPILLARY NETWORK SHOULD BE EXPECTED (AFTER SECHER)

length and particularly their width increase as well. Another result of the stasis is that a few deeper, small vessels become visible. Similar and undoubtedly similarly caused conditions are observed in many

heart patients with increased venous pressure. The cause of the increase in the size and number of visible capillaries in these cases of cyanosis is undoubtedly the increase in the local blood volume, whereas in the cyanosis caused by cold the increased amount of blood is secondary to a dilatation or paralysis of the capillaries. Also in

FIG. 9. CAPILLARIES IN A NORMAL INDIVIDUAL. NAIL WALL (AFTER BOAS)

polycythemic patients (including some of the congenital heart lesions) an increase in the number and width of the capillaries is observed. Associated with this is an increase in the total blood volume as shown by Bock and Means. Probably there is also a hyperplastic condition of the capillary system. In acrocyanosis of different origin, increased width and length of the capillaries have been found by Weiss and Holland; Henius; Halpert; and Boas. Figures 9 and 10, which

are from Boas' publication, illustrate the difference between the capillaries of a normal individual and of a patient with acrocyanosis of unknown etiology. In artificial stasis, in heart diseases with stasis, in acrocyanosis, and in polycythemic plethora, conditions therefore exist which increase the influence of one of the modifying factors, viz., the proportion of skin capillaries that are filled with blood, and the degree to which the capillaries are distended.

FIG. 10. CAPILLARIES FROM A PATIENT WITH ACROCYANOSIS. NAIL WALL (AFTER BOAS). FIGS. 9 AND 10 WERE MADE ON THE SAME SCALE

In pernicious anemia (but not in chlorosis) the opposite conditions have been observed by Schur, Jürgensen, and particularly by Hisinger-Jägerskiöld. Not only is the number of blood-filled capillaries fewer but they are thinner than usual. Hisinger-Jägerskiöld has observed that the venous part of the capillary loop and the "Schaltstück" (Jürgensen) are not broader than the arterial, as

they usually are under normal conditions. The principal cause of this condition is possibly a decrease in the total blood volume of the body. The scarcity and slenderness of the skin capillaries are usually proportional to the degree of anemia. In a few instances of cured pernicious anemia (Bothriocephalus anemia) Hisinger-Jägerskiöld found the same conditions as in the anemic stage. This led him to suggest the possibility of a hypoplastic development of the capillary system in these patients. In such cases the effect of the modifying factor is to diminish the influence of the blood on skin color and to decrease the tendency to cyanosis. It would be desirable in order to ascertain the relative importance of this factor in modifying the color produced by capillary unsaturation, to obtain in normal and cyanotic individuals information not only about the number and width of the capillaries for a given skin area but also about the increase in the number and width for a given increase in venous and capillary pressure, because an increased venous pressure is common in many cyanotic patients with circulatory disturbances.

The last mentioned factor, *the shape of the reduction curve of the oxyhemoglobin during the passage of the blood through the tissue capillaries* is probably also important. Unfortunately, little is known about it, and it does not seem very likely that much information on the question can be obtained.

If we assume the mean capillary unsaturation $\frac{A+V}{2}$ as the average unsaturation of the capillary blood, it is obvious that this is only an approximation. Certain factors tend to make the greater part of the capillary blood approximate the venous, while others tend to make it approximate the arterial. The value $\frac{A+\dot{V}}{2}$ would represent exactly the average capillary unsaturation only if the blood in passing through each capillary lost a constant amount of oxygen per unit of capillary length traversed (i.e., losing one-fourth of the total oxygen loss in passing the first one-fourth of the capillary's length, etc.). This behavior would be represented by the straight line I (fig. 11).

It is quite certain that the straight line I does not exactly represent the conditions existing in the capillaries. When the arterial blood first enters the capillary, the oxygen tension difference between the

capillary blood and the tissues is greatest, and it becomes increasingly less as the blood progresses along the capillary towards the venous end. This factor would tend to make oxygen loss most rapid at the arterial end of the capillary and least at the venous, the course of oxygen loss being represented by a concave curve, like III (fig. 11). However, another factor tends to have the opposite effect, namely the form of the oxygen dissociation curve of the blood (Barcroft, a, p. 65). Because of this form, as the oxygen tension falls from arterial to venous, each succeeding given drop in tension results in a greater loss of oxygen content than the preceding. Thus, with 40 mm. CO_2 tension, Barcroft's blood in falling from 100 to 80 mm. oxygen tension, lost only about 2 per cent of its maximum total oxygen, whereas falling from

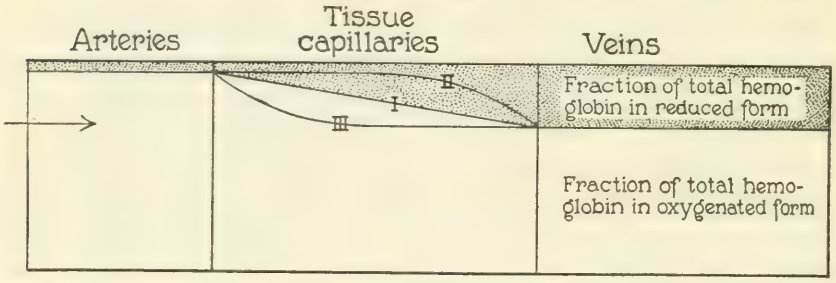

FIG. 11. DIAGRAM SHOWING HYPOTHETICAL VARIATIONS IN THE SHAPE OF THE REDUCTION CURVE OF OXYHEMOGLOBIN DURING THE PASSAGE OF THE BLOOD THROUGH TISSUE CAPILLARIES

40 to 20 mm. it lost about 40 per cent. This factor will tend to make the curve of oxygen loss along the capillary assume the form II, the most rapid loss occurring toward the venous end, at the lowest oxygen tensions. A third factor is the influence of carbonic acid. Because of the interaction of CO_2 and O_2 (Bohr; Christiansen, Douglas, and Haldane; L. J. Henderson; D. D. Van Slyke), CO_2 entering the capillaries from the tissues must react with the hemoglobin and thereby raise the oxygen tension. This effect would presumably tend to give a course of oxygen loss following curve III. Furthermore, low velocity of capillary flow, as directly observed by capillaroscopy in several instances of acrocyanosis (Carrier, Boas, and others), might be expected to result in most of the oxygen loss occurring near the arterial end of the capillary (curve III).

If the combined effect of all factors results in most rapid loss of oxygen in the arterial end of the capillary (curve III), then the greater part of the capillary blood will approximate the venous in oxygen content, and the formula expressing the average unsaturation of the capillary blood, instead of simply $\frac{A + V}{2}$, will be $\frac{A + nV}{1 + n}$, n being greater than 1. If, on the other hand, loss of oxygen is most rapid at the venous end of the capillary (curve II), the average capillary blood will be more nearly arterial than venous, and n of the above formula will be less than 1. Since it is impossible from data now available to know what condition prevails, we have, in relating cyanotic color to the content of reduced hemoglobin in the capillary blood, assumed the simplest relation, namely that $n = 1$, and the average unsaturation of the capillary blood is midway between that of the arterial and venous bloods respectively (curve I).

FACTORS INFLUENCING THE CONCENTRATION OF REDUCED HEMOGLOBIN IN THE CAPILLARY BLOOD

There are certain factors concerning which, unlike the above, we are able to obtain more or less exact information, and whose influence on the mean capillary unsaturation can be predicted with some degree of numerical accuracy. We shall briefly outline these factors in the following paragraphs, and in figures 12, 13, 14, and 15.

Figure 12 represents the circulatory conditions in a normal resting individual. The width of the band represents 20 volumes per cent of oxygen capacity (i.e., 15 grams of hemoglobin per 100 c.c. of blood, footnote 4, p. 8). The blood emerging from the lungs is 95 per cent saturated, contains 19 volumes per cent of oxygen, and has an unsaturation of 1 volume per cent. In passing through the tissue capillaries, the blood loses 5 volumes per cent of oxygen, and emerges with 14 volumes per cent of oxygen[5] and 6 volumes per cent of

[5] The oxygen normally present in the venous blood (about 14 volumes per cent) has been termed the reserve oxygen (Lundsgaard, 1919, e). It is in some ways to be looked upon as analogous to the reserve power of the heart. Its significance for the efficiency of the circulation is not yet clearly understood. According to observations of Lundsgaard and Möller (a) it appears possible that the reserve oxygen is taken into use during exercise not only in the working organs themselves, but through vasomotor action also in the resting parts of the body. This may be of importance for the topographic distribution of cyanosis as will be discussed later.

unsaturation. The mean unsaturation, C, of the capillary blood is $C = \frac{1 + 6}{2} = 3.5$ volumes per cent. The saturation of the blood with oxygen in the lungs is represented in our diagram by a straight line, although it is unlikely that this represents the actual course of

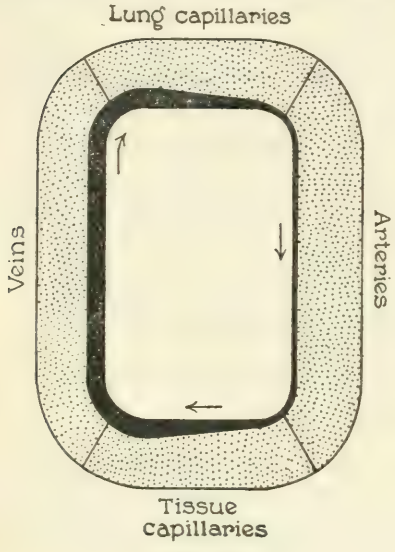

Fig. 12

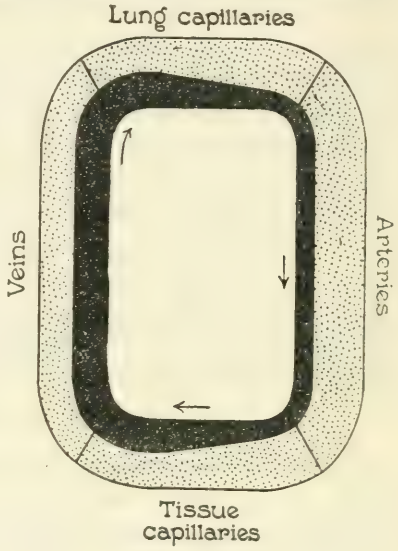

Fig. 13

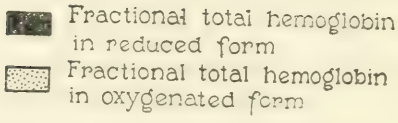

Fig. 12. Diagram Showing the Proportion of Oxygenated Hemoglobin to Reduced Hemoglobin in Different Parts of the Circulatory System in Normal Resting Individuals

Fig. 13. Diagram Showing the Proportion of Oxygenated to Reduced Hemoglobin in Different Parts of the Circulatory System in a Case of Incomplete Oxygenation in Aerated Parts of the Lungs

resaturation. For the present considerations this is, however, of no moment.

The arterial blood has, of course, the same composition in all the arteries, and we are correct in representing the arterial stream by a band of uniform width (figs. 12 to 15). The proportion between reduced

and oxidized hemoglobin, viz., 1 to 19, is indicated to be the same at all points of the arterial stream. Such constancy does not hold true for the venous blood; blood coming from different regions into different veins is reduced in different degrees. In spite of this fact, we have represented the venous blood stream in figures 12 to 14 by a single band which gives the average composition of the venous blood as we find it in the central veins. Figure 15 indicates how the venous blood from different parts may be of different composition. Because of this variation local cyanosis may occur where high local deoxidation causes a greater mean capillary unsaturation than the average.

Figures 13 and 14 distinguish between two conditions which lower the oxygen saturation of the arterial blood. Figure 13 represents a condition in which, although all the blood in passing from the right heart to the left traverses lung tissue anatomically accessible to inspired air, the diffusion of oxygen from the inspired air into the blood is so hindered that oxygenation is incomplete. Conditions causing such hindrance may be classified as (1) those involving low oxygen tension in the alveoli (high altitude, inefficient ventilation), and (2) those retarding diffusion of oxygen from the alveoli into the blood. Such retardation would depend on a decreased diffusion rate of oxygen through the alveolar walls.

Of the two causes mentioned of low alveolar oxygen tension, altitude requires no discussion. The rôle of inefficient ventilation is not so obvious. However, it appears self-evident that extremely shallow respiration, such that the inspired air is hardly more than enough (about 150 c.c.) to fill the dead space, must leave the gas exchange between alveoli and external air to be accomplished to a greater extent than normally by mere diffusion through the bronchial tubes, rather than by inflow and outflow of air. Under such conditions of retarded exchange one could not expect the oxygen tension in the alveoli to be kept as near as normal to the tension in the external atmosphere. Haldane, Meakins, and Priestley have found that "shallow breathing causes uneven ventilation of the lungs and this in turn produces anoxæmia." Meakins (a, b, and c) explains the cyanosis of pneumonia as due to such shallow breathing.

The second cause mentioned for the condition indicated in figure 13, viz., decreased permeability of the alveoli due to physical conditions

(presence of fluid, thickening of alveolar walls), is as yet a purely hypothetical possibility. It has been suggested, however, as a cause for the cyanosis, or susceptibility to cyanosis on slight exertion, observed in bronchopneumonia (Hoover), and in war gas poisoning (Barcroft, Hunt, and Dufton). Lately, Brauer has introduced the term pneumonosis to indicate a decreased permeability of the alveolar epithelium. In this way he explains the cyanosis which he observed in influenza patients before any anatomical lesions of the lungs could be detected. Marie Krogh introduced a method for the determination of diffusion constants, and obtained normal results in 4 patients with emphysema or with asthma, 1 with tuberculosis, and 3 with pneumonia. Whether a pathologically lowered diffusion constant for the alveolar membranes ever actually occurs is therefore not yet directly shown.

Another, but purely theoretical, possibility is that the blood can go so fast through the lungs (exercise, lung impairment) that an appreciable decrease in the normal saturation of the arterial blood results. The few experiments hitherto published on this subject show that a slight decrease in arterial oxygen saturation (about 1 to 2 volumes per cent), may take place during very strenuous exercise (Barcroft, Harrop). However, we do not know whether this is caused by difficulty in keeping up the alveolar oxygen tension, by increased acidity of the blood, or by the rapid blood flow itself.[6]

Figure 14 represents a condition in which part of the blood in the passage from the right heart to the arteries traverses a path to which access of air is anatomically impossible. Such a condition is observed in patients with congenital perforate septum of the heart, where a fraction of the blood is shunted directly from the right heart to the left, without passing through the lungs. It also occurs when anatomical obstruction prevents access of inspired air to any part of the lungs through which blood continues to flow.

Presumably the reason why one entire lung may be collapsed by pneumothorax or by pleuritic exudate, or almost filled with exudate in pneumonia, without occurrence of cyanosis, is that less than the normal half of the blood flows through the unaerated lung in these conditions;

[6] In a yet unpublished study Barr and Himwich have found a slight increase in the oxygen saturation of the arterial blood during and shortly after heavy exercise in man (personal communication added to proof).

and as will be shown later, about one-third of the blood may be shunted through an unaerated path from the right heart to the arteries before sufficient unsaturation results to cause cyanosis. In cases of exudative pleurisy and of pneumothorax in which an entire lung is compressed so as to prevent aeration, it appears probable that the pressure in

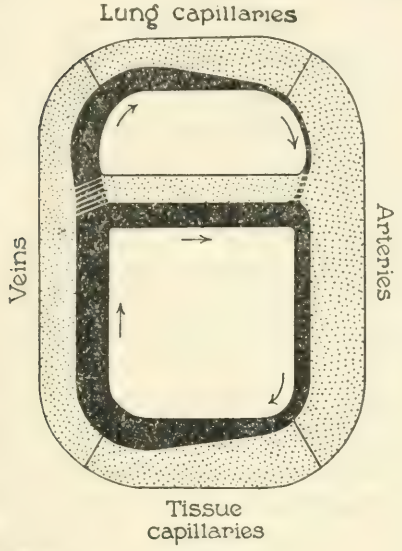

Fig. 14

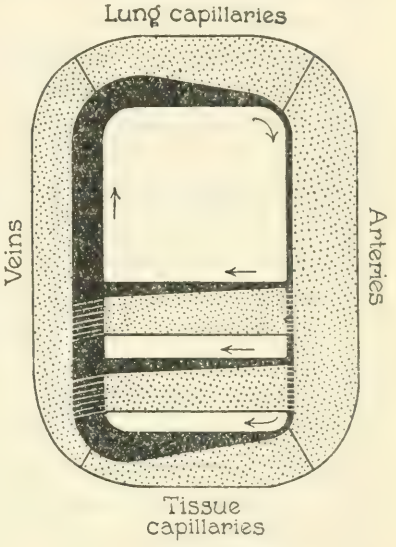

Fig. 15

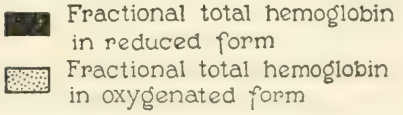

FIG. 14. DIAGRAM SHOWING THE PROPORTION OF OXYHEMOGLOBIN TO REDUCED HEMOGLOBIN IN DIFFERENT PARTS OF THE CIRCULATORY SYSTEM IN A CASE WHERE A FRACTION OF BLOOD PASSES THROUGH UNAERATED CHANNELS FROM VENOUS TO ARTERIAL SYSTEM

FIG. 15. DIAGRAM SHOWING THE PROPORTION OF OXYHEMOGLOBIN TO REDUCED HEMOGLOBIN IN DIFFERENT PARTS OF THE CIRCULATORY SYSTEM IN A CASE WHERE DEOXIDATION IS ABNORMALLY HIGH IN A PART OF THE PERIPHERAL CAPILLARIES AND NORMAL IN OTHER PARTS

the pleural sac exceeds that in the pulmonary artery, so that circulation from the latter is entirely cut off. In a patient with total compression of one lung from a large pleuritic exudate, Lundsgaard and

Möller (b) found that the cutaneous blood was 96 per cent saturated with oxygen, indicating that the compression of the lung had been so complete that not only aeration but also circulation had been prevented.

In pneumonia, conditions governing the blood flow through consolidated parts are variable. In typical lobar pneumonia when gray hepatization occurs the parts are almost bloodless. Patients of this type show much less tendency to become cyanotic than those with the type of bronchopneumonia frequently encountered in influenza, in which the lungs on section are found red and full of blood. Bronchopneumonia in children is also a condition where cyanosis is frequent, and in which the lungs are full of blood.

Although the result, deficient oxygenation of the arterial blood, is the same whether caused by incomplete alveolar oxygenation (fig. 13) or by an unaerated shunt of venous blood into arterial (fig. 14), yet it is of some importance to distinguish between the two causes. Differentiation between them may be difficult or even impossible in many cases. It may, however, influence both diagnosis and therapy.

In a case of retarded alveolar oxygenation (fig. 13), respiration of air with an increased oxygen concentration would increase the alveolar oxygen pressure and thereby the diffusion rate, with a resultant increase in the oxygen content of the arterial blood. Hence the efficacy of the oxygen treatment in mountain sickness, in gas poisoning, and in pneumonia (Haldane, 1917; Means and Barach, 1921; Barach and Woodwell, 1921; and Stadie, 1922).

In an unaerated shunt, on the other hand, with access of air completely prevented by anatomical obstruction, it is obvious that increase in oxygen tension of the inspired air could cause no oxygen absorption. In a case with such a shunt oxygen administration would only increase slightly the already nearly maximal oxygen content of the fraction of blood passing through aerated lung areas. The main cause of arterial unsaturation, venous blood shunted through an unaerated channel, would be unaffected.

It is a fact that may at first glance appear curious, that while an unaerated shunt prevents complete oxygenation of the arterial blood, the CO_2 tension and the pH of the blood may nevertheless be kept within normal limits. As pointed out by Haldane, Meakins,

and Priestley, by very rapid ventilation of the aerated lung areas the blood passing through them may have its CO_2 content so greatly reduced that when it rejoins the blood from the unaerated parts the mixture has the CO_2 tension and content of normal arterial blood. Hyperventilation of part of the blood can compensate, in CO_2 excretion, for entire lack of ventilation of the remainder; but because of the blood's limited oxygen capacity, it cannot compensate for entire lack of oxygenation in any considerable part of the stream.

We have above sharply differentiated between deficient pulmonary oxygenation (due usually to low alveolar oxygen tension) and the passage of venous blood into arterial through entirely unaerated channels, as causes of reduced hemoglobin in the arterial blood; and such sharp differentiation appears of assistance in classifying the causes of cyanosis and in calculating their relative influences on it. It is probable, however, that intermediate conditions exist, in which parts of the lungs although not absolutely separated by anatomical obstructions from the well aerated parts, are rendered so difficult to access by air that what one might term a functional shunt exists. The diffusion of air into such parts might be so slow and the oxygen tension reduced so nearly to that of venous blood that the effect would more or less closely approach that of complete separation from inspired air. Inspiration of air enriched with oxygen might raise the arterial oxygen content to more nearly normal than it would in a person with a completely unaerated shunt between veins and arteries, but not restore it entirely to normal. It is quite possible that such partially unaerated shunts occur in pneumonia, due either to partial bronchial obstruction or to the very shallow breathing.

Figure 15 represents the results of increased reduction of the oxygen during flow through the tissue capillaries. This would be caused either by decreased rate of flow through the capillaries, or by increased rate of oxygen consumption by the tissues. Decreased rate of capillary flow as a sole cause of cyanosis has been experimentally demonstrated only as a local condition. Cyanosis is a familiar occurrence when stasis is caused by ligating an extremity, and thereby retarding the capillary flow by venous back pressure. Lundsgaard (c) found that in a normal individual with a ligated arm, cyanosis began to appear in the arm and hand when the venous oxygen unsaturation

reached 10.2 volumes per cent. If we assume 1 volume per cent of arterial unsaturation, the mean capillary unsaturation was $C = \frac{10.2 + 1.0}{2} = 5.6$ volumes per cent.

In the local cyanosis caused by chilling the arm, Meakins and Davies found that when an arm became faintly bluish the unsaturation of the venous blood rose to 65.1 per cent of total capacity (which was 17.48 volumes per cent). The venous unsaturation was therefore $0.651 \times 17.48 = 11.4$ volumes per cent. The arterial was 0.7. The mean capillary unsaturation was, therefore, $C = \frac{11.4 + 0.7}{2} = 6.05$ volumes per cent, which is at the lower limit of the range (6 to 7 volumes per cent) of capillary unsaturation which Lundsgaard found to be usually associated with cyanosis. A very blue color was observed when the venous blood was entirely reduced, and $C = \frac{17.5 + 0.7}{2} = 9.1$ volumes per cent.

Another, theoretically possible, cause of retarded capillary flow and consequently increased capillary and venous unsaturation is a decreased minute output of the heart. That capillary flow may be so retarded by this cause that the latter by itself produces cyanosis, has not yet been definitely demonstrated. It probably is a contributing cause. Direct and indirect evidence has been obtained by several investigators that the resting minute volume of the heart is lowered in cardiac decompensation (Stewart; Hewlett; Means and Newburgh; Lundsgaard, a and b). Whether such retardation, by itself alone, is sufficient to raise the mean capillary unsaturation above the threshold for cyanosis is, however, uncertain. That many decompensated cardiac patients are cyanotic is certain. Lundsgaard and Möller (a) have suggested that patients with impaired heart function and decreased minute volume might be able to compensate to a certain degree for lack of reserve power of the myocardium by an abnormal distribution of the blood flow (through increased action of the vasomotor mechanism), providing in this way sufficient perfusion in some organs at the cost of the local blood flow in other organs. In this way the local results of a diminished minute volume of the heart

might be magnified in some regions, and local cyanosis possibly occur, partly as direct, partly as an indirect result of the decreased outflow from the heart.

QUANTITATIVE INFLUENCES OF THE DIFFERENT FACTORS CONTRIBUTORY TO THE PRESENCE OF REDUCED HEMOGLOBIN IN THE CAPILLARY BLOOD

The degree of cyanotic color developed by a given concentration of reduced hemoglobin is influenced by modifying factors, previously discussed, such as skin pigmentation and vascularity, which at present are not capable of quantitative consideration. Their variability must be allowed for by attributing a wide range, probably at least from 5 to 8 volumes per cent, to the threshold of mean capillary oxygen saturation at which cyanosis becomes evident. While the factors *modifying* the cyanotic color can be handled only by thus allowing for their variability, the factor *causing* the color, viz., the concentration of reduced hemoglobin in the skin capillaries, represents the summation of certain definite contributory factors which are to some degree susceptible of quantitative measurement or calculation. Reduced hemoglobin in the venous and arterial blood, and hence in the capillary, results primarily from two respective causes, oxygen consumption in the tissues and incomplete reoxygenation in the lungs. The magnitude of the effect of each may be influenced by a secondary factor.

The total hemoglobin content is such a factor. If reoxygenation in the lungs leaves a given fraction of hemoglobin in the reduced form (as is the case with a given lowered alveolar oxygen tension, for example), it is obvious that the resulting concentration of reduced hemoglobin is proportional to the total content of hemoglobin present, since it is a definite fraction of the latter. Consequently, the effect of deficient pulmonary ventilation on the content of reduced hemoglobin in arterial blood is proportional to the total hemogobin content, which is therefore an influencing, secondary factor.

The effect of oxygen consumption in the tissues is similarly influenced by a secondary factor, the fraction of blood traversing an unaerated shunt from right heart to arteries. Such a shunt pours some of the venous blood directly into the arterial. Consequently, deoxygenation in the tissues causes not only venous unsaturation but

also some arterial unsaturation. Thereby the effect of tissue deoxygenation on the capillary unsaturation is augmented beyond what it would be if all the hemoglobin were reoxygenated before reaching the arteries. In this case, deoxygenation of blood in the tissue capillaries increases not only V but also A, which together determine the mean capillary unsaturation $\left(C = \frac{V + A}{2}\right)$.

There may therefore be four factors involved in increasing the capillary content of reduced hemoglobin, viz.: (1) deficient pulmonary oxygenation, the effect of which is proportional to (2) the total hemoglobin content, and (3) during passage of the tissues, increased oxygen consumption, the effect of which may be augmented by (4) the presence of an unaerated channel through which venous blood reaches the arteries.

The quantitative effects of these four factors are indicated by a formula developed as follows:

Let

T = total hemoglobin content of the blood.

A = reduced hemoglobin content of arterial blood.

V = reduced hemoglobin content of venous blood.

D = content of hemoglobin deoxygenated in passage of blood from arteries to veins ($D = V - A$).

l = fraction of total hemoglobin passing in reduced form through *aerated* portions of lungs.

α = fraction of total blood shunted through *unaerated* channels from right heart to arteries.

C = mean reduced hemoglobin content of capillary blood.

The mean reduced hemoglobin content of the capillary blood is expressed as explained before by the equation

$$C = \frac{A + V}{2} \tag{1}$$

When there is no unaerated shunt, and $\alpha = 0$, we have the relationship

$$A = lT \tag{2}$$

This simply expresses the fact that since all the arterial blood passes through aerated parts of the lungs in going from the right heart to the

left, the content, A, of reduced hemoglobin in the arterial blood is equal to lT, the product of the total hemoglobin content, T, multiplied by the fraction of hemoglobin, l, still in the reduced form on entering the arteries.

However, when a certain proportion, α, of the blood, is shunted through a perforate septum in the heart, or through unaerated portions of the lungs, A exceeds lT, because a fraction, α, of blood with the higher reduced hemoglobin content, V, of venous blood, is mixed with $1 - \alpha$ part of aerated pulmonary blood, with lT content, to form the arterial blood, with reduced hemoglobin content A between lT and V. The exact relationships in such a case are indicated by equation (3).

$$A = (1 - \alpha)\, lT + \alpha V \tag{3}$$

If (3) is solved for α, we obtain:

$$\alpha = \frac{A - l\,T}{V - l\,T} \tag{4}$$

This is an expression which may be of use in estimating the value of α experimentally.

To express α in terms of V and D, instead of V and A, we substitute $V - D$ for A in (4) and obtain

$$\alpha = \frac{V - D - l\,T}{V - l\,T} \tag{5}$$

Solving (5) for V we obtain

$$V = l\,T + \frac{D}{1 - \alpha} \tag{6}$$

Similarly, we substitute $A + D$ for V in (4) and obtain

$$\alpha = \frac{A - l\,T}{A + D - l\,T} \tag{7}$$

Solving (7) for A we obtain

$$A = l\,T + \frac{\alpha\, D}{1 - \alpha} \tag{8}$$

We now substitute for A and V in equation (1) their values as expressed in (6) and (8), and thereby obtain (9), which shows the quantitative effects on C of all four factors considered.

$$C = l\,T + \frac{(1 + \alpha)\, D}{2\,(1 - \alpha)} \tag{9}$$

Equation (9) also indicates the manner in which, as stated before in words, T influences the effect of l, and α the effect of D on C.

SEPARATE EFFECTS OF THE INDIVIDUAL FACTORS CONTRIBUTING TO THE REDUCED HEMOGLOBIN OF THE CAPILLARY BLOOD

In order to illustrate the effect of each of the four factors we have calculated C, assuming in turn that one factor at a time undergoes the extreme possible variations while the others remain normal. Expressing reduced hemoglobin concentration in terms of volumes per cent of oxygen unsaturation, and hemoglobin content, T, also in oxygen terms as total oxygen capacity, we have taken as the normal figures, $T = 20$, $D = 5$, $l = 0.05$, $\alpha = 0$.[7] If we keep T, D, and l at these values, permit α to vary from zero towards 1, and calculate the corresponding C values, we obtain the curve on figure 16 marked α. In a similar way the curves l, D, and T are obtained.

For l, D, and T the ordinary ranges of the values for a normal resting adult (D may normally be increased by exertion) are indicated by brackets on their respective curves (α normally is zero).

It becomes obvious from a glance at figure 16 that the factor which, in proportion to its deflection from the normal, has the greatest effect in producing capillary oxygen unsaturation, is l.

When this fraction reaches 0.2, *the other factors remaining normal*, the mean capillary oxygen unsaturation reaches 6.5 volumes per cent, at which cyanosis usually appears. As a matter of fact, Barcroft and his party in the Andes (1922) found that cyanosis did appear when the oxygen unsaturation of arterial blood reached 15 to 20 per cent of the total capacity. Binger, Hastings, and Neill found cyanosis appearing in a pneumonia patient also at about this range of arterial oxygen unsaturation. The absence of an unaerated shunt in this patient was demonstrated by the fact that doubling the oxygen tension in the inspired air raised the arterial oxygen saturation to normal.

[7] Values for T, A, V, D, and C, can all be expressed in volumes per cent (see footnote 4). That T is 20 volumes per cent, means that hemoglobin is present in the blood in such a concentration (15 grams per 100 c. c. of blood) that 20 c. c. of oxygen can combine chemically with 100 c. c. of blood. A value for D of 5 volumes per cent, means that 5 c. c. of oxygen per 100 c. c. of blood has been taken away from the blood during its passage through the tissue capillaries. l and α are expressed simply as fractions of T and of the total blood flow per minute, respectively. A value of 0.05 for l means that the oxygenation of the blood in the aerated part of the lungs is 95 per cent of its maximal value. That α is 0.3 means that 30 per cent of the blood going to the right side of the heart passes through an unaerated channel to the left side.

The factor of second importance, regarded from the proportion of its maximum extent that must be reached to cause cyanosis, is α, the fraction of blood passing through unaerated channels from right

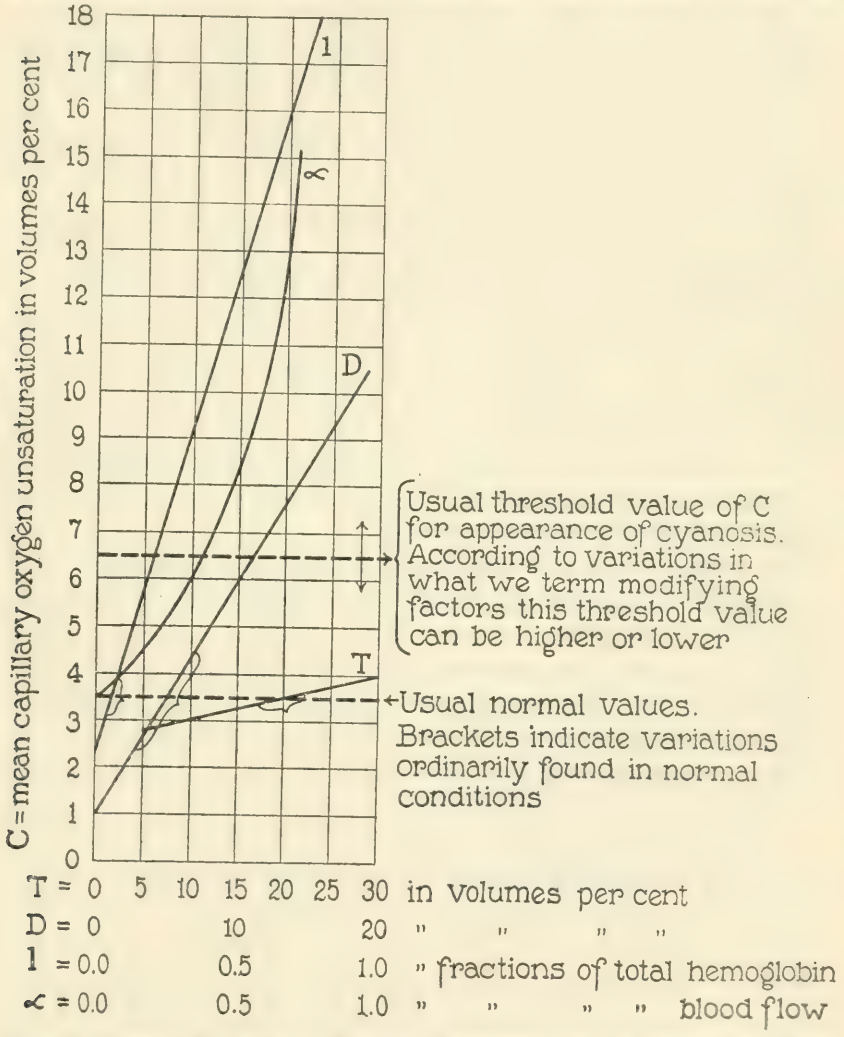

FIG. 16. DIAGRAM SHOWING THE RELATIVE MAGNITUDE OF THE INFLUENCE ON MEAN CAPILLARY OXYGEN UNSATURATION (*C*) OF VARIATIONS IN TOTAL OXYGEN COMBINING POWER OF THE BLOOD (*T*), IN DEOXIDATION RATE DURING THE PASSAGE OF BLOOD THROUGH THE CAPILLARIES (*D*), IN THE FRACTION OF TOTAL HEMOGLOBIN PASSING UNOXIDIZED THROUGH AERATED PARTS OF THE LUNGS (*l*), AND IN FRACTION OF BLOOD (α) PASSING FROM RIGHT TO LEFT THROUGH CHANNELS TO WHICH AIR HAS NO ACCESS

heart to arteries. From figure 16 it is evident that, other factors remaining normal, α may become as great as one-third of the total blood stream before what may be termed the cyanotic threshold is crossed. That so much venous blood could be mixed with arterial before cyanosis appears was not recognized by past investigators of cyanosis, and in consequence there arose much confusion in the field, the occurrence of any unaerated shunt at all without cyanosis being accepted by some as proof against such a shunt as a possible cause (see historical discussion, page 64).

The third factor in its relative isolated influence on the capillary mean content of reduced hemoglobin is D, expressed as volumes per cent of oxygen taken from the blood in its passage from arteries to veins. D is normally about 5 volumes per cent. Its theoretical maximum with 20 volumes per cent total oxygen capacity, 1 volume per cent arterial unsaturation, is of course 19. And with the other factors all normal, it can rise to about 12, or over 0.6 of this, before C crosses the cyanotic threshold. It becomes comprehensible, why, in normal individuals, the venous oxygen may fall unusually low without the occurrence of cyanosis.

It is obvious from figure 16 that changes in the fourth factor, T, the total hemoglobin content, have relatively slight effect on the capillary reduced hemoglobin content. As pointed out before, however, (page 27) the total hemoglobin content does determine the effect on C of deficient pulmonary oxygenation (high value of l). Similarly, the value of D, through its influences on V, determines the effect of α on C. The quantitative nature of the effect on C of combinations of l, T, D, and α, respectively, forms the subject of the next paragraphs.[8]

[8] The effects on C of separate variations of l, T, D, and α, shown graphically by the curves of figure 16, are shown in a more general way by partial differentiation of equation (9) with respect to each factor in turn. Thus we obtain:

$$\delta C = T \delta l \tag{10}$$

$$\delta C = l \delta T \tag{11}$$

$$\delta C = \frac{D}{(1-\alpha)^2} \delta \alpha \tag{12}$$

$$\delta C = \frac{1+\alpha}{2(1-\alpha)} \delta D \tag{13}$$

(10) and (11) bring out the effect of T on the result of l changes, and vice versa, while (12) and (13) do the same for α and D.

COMBINED EFFECTS OF THE FACTORS CONTRIBUTING TO THE PRESENCE OF REDUCED HEMOGLOBIN OF THE CAPILLARY BLOOD

As pointed out in the previous pages from a consideration of the physiological relations, a given degree of deficiency (l) in oxygenation of the pulmonary blood produces an amount of reduced hemoglobin proportional to the total hemoglobin present (T). And the further amount of reduced hemoglobin in the circulation produced by a given consumption in the tissues (D) is magnified by the pouring of a part (α) of the deoxygenated venous blood through an unaerated channel into the arteries. The total reduced hemoglobin produced is the sum of that due to l and T acting together (this amount being represented in equation (9) by the term lT), plus that due to D and α acting together $\left(\text{represented by the term } \frac{(1 + \alpha)\ D}{2\ (1 - \alpha)}\right)$. While, therefore, we would be correct in merely adding the separately calculated effects on C of given increases in l and D, we could not, when l and T both vary, calculate separately the effects of given increases in each, such as might be estimated by interpolations on the l and T curve of figure 16, and by adding the increases there found, correctly estimate the resultant C. A given increase in T augments the effect of a given increase in l and vice versa; and α and D are likewise related. Consequently, for a view of the influences of the factors when more than one at a time is abnormal it is necessary to consider them not singly, but in pairs, l and T being treated together because of their mutual influence on each other, and likewise D and α.

A. Combined effect of simultaneous variations in pulmonary oxygenation (l) and in hemoglobin content (T)

We have expressed in figure 17 the volumes per cent of capillary oxygen unsaturation produced by variations in l and T together, calculated as $C = lT$. In figure 17 we have indicated also the total C that would result from the effect of these factors added to the effect of a normal D of 5 with $\alpha = 0$. It is obvious that the reduced hemoglobin content, C, in the capillaries produced by passage through the lungs of a given hemoglobin fraction l in the reduced form is dependent on the total hemoglobin content T. The values of l which pro-

duce the capillary unsaturation usually necessary for cyanosis to become apparent, viz., 6.5 volumes per cent, are, from figure 17, the following:

T HEMOGLOBIN CONTENT	l TO PRODUCE $C = 6.5$ FRACTION OF HEMOGLOBIN PASSING LUNGS IN REDUCED FORM
volume per cent oxygen capacity	
5	Impossible for C to be as great as 6.5
10	0.40
20	0.20
30	0.15

From the above table it is evident that a person with only 25 per cent of normal hemoglobin ($T = 5$) can ordinarily not become cyanotic, and one with 50 per cent becomes cyanotic from deficient pulmonary oxygenation only when the deficiency is so great as to permit about 40 per cent of the hemoglobin to pass the lungs unoxidized. A polycythemic person, on the other hand, with $T = 30$, would pass the usual cyanotic threshold, $C = 6.5$, when the blood left his lungs with only 15 per cent of its hemoglobin unoxygenated.

The nature of the combined effects of deficient pulmonary oxygenation and blood hemoglobin concentration on the production of cyanosis appears hitherto to have escaped notice, with some resulting confusion in the interpretation of clinical observations. The reason for the readiness of polycythemic patients to become cyanotic has not been understood, and polycythemia in itself has been considered as a cause of cyanosis. As illustrated by figure 17, polycythemia can markedly enhance the cyanotic effect of deficiency in oxygenation.

It is evident, therefore, that the presence and extent of deficient pulmonary oxygenation cannot be judged with any degree of accuracy from the skin color produced unless the other factors, D, α, and T, but especially the hemoglobin content, T, are taken into consideration.

Another point of interest in this connection is that a person who becomes polycythemic because of the well known physiological increase in hemoglobin at high altitudes, might show a cyanosis in the rarefied atmosphere, while cyanosis might not be evident in a normal or anemic person with the same fraction of reduced hemoglobin in his arterial blood. In this case the cyanotic individual would be the one in better physiological condition.

The influence of venesection in clearing up cyanosis is doubtless due to some extent to the lowering of the hemoglobin content, although the main factors are probably reduction in D due to improved circula-

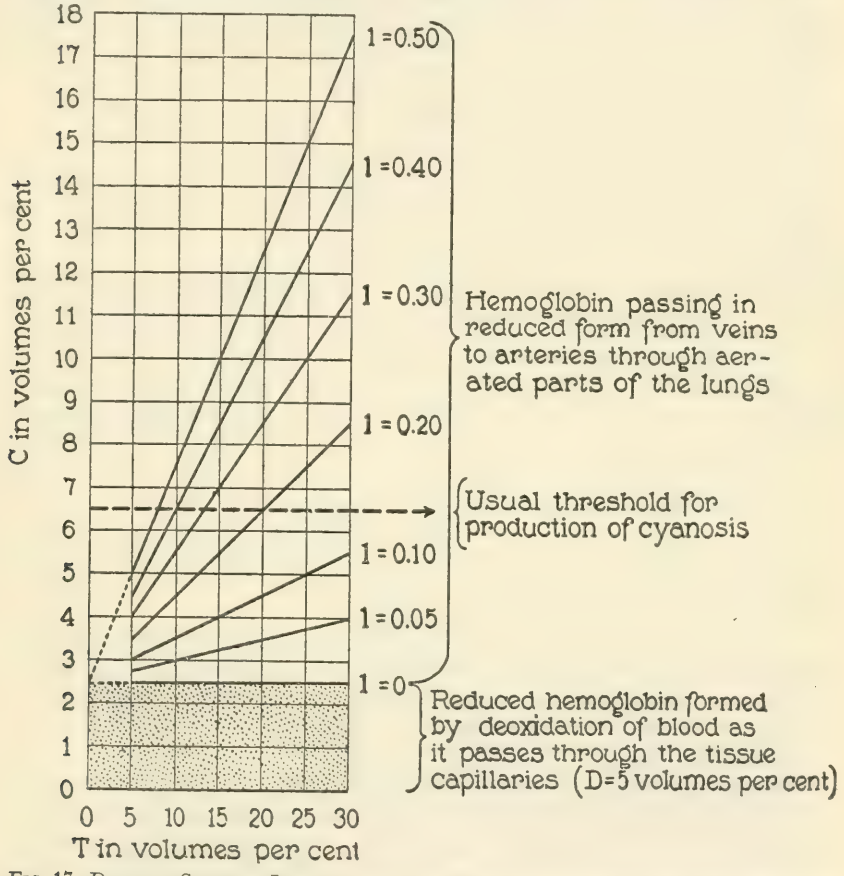
C in volumes per cent
T in volumes per cent
0 5 10 15 20 25 30
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
l = 0.50
l = 0.40
l = 0.30
l = 0.20
l = 0.10
l = 0.05
l = 0
Hemoglobin passing in reduced form from veins to arteries through aerated parts of the lungs
Usual threshold for production of cyanosis
Reduced hemoglobin formed by deoxidation of blood as it passes through the tissue capillaries (D=5 volumes per cent)

FIG. 17. DIAGRAM SHOWING INFLUENCE ON THE MEAN CAPILLARY OXYGEN UNSATURATION (C) OF SIMULTANEOUS VARIATIONS IN T AND l

tion and in l due to relief of pulmonary stasis. This procedure may, by relieving peripheral stasis, also diminish the effect of one of the modifying factors, the distension of the capillaries.

B. Combined effect on C of simultaneous variations of the oxygen consumption (D) and the fraction of blood shunted (α)

The influence of D on the capillary unsaturation is in most instances mainly local on account of the great variations of blood flow in the

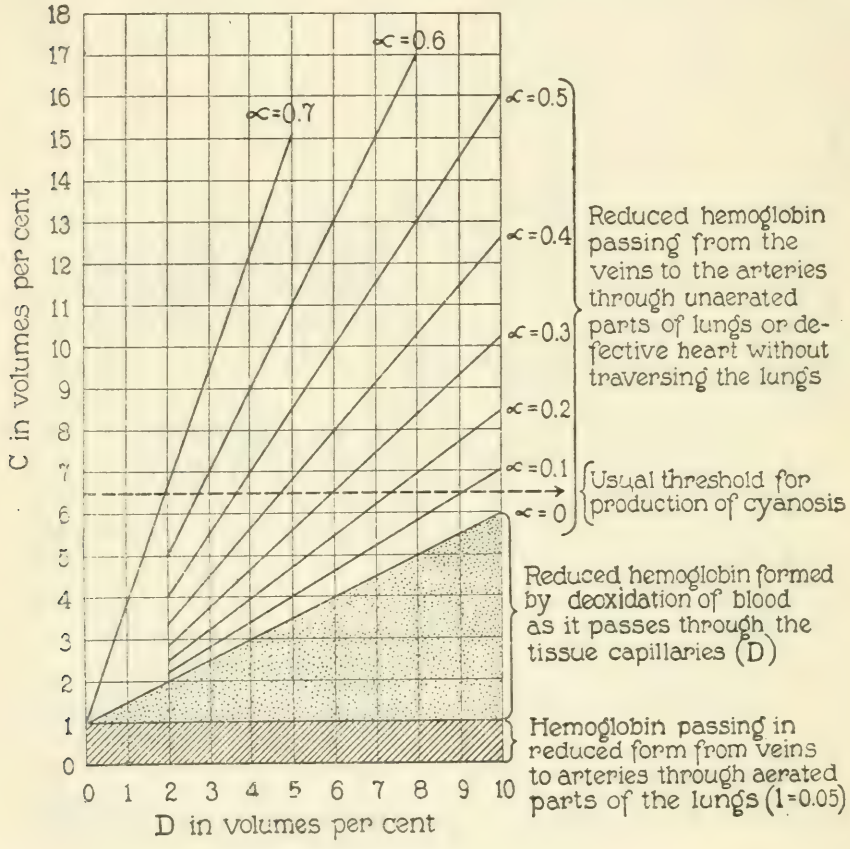
C in volumes per cent
D in volumes per cent
∝=0.6
∝=0.7
∝=0.5
∝=0.4
∝=0.3
∝=0.2
∝=0.1
∝=0
Reduced hemoglobin passing from the veins to the arteries through unaerated parts of lungs or defective heart without traversing the lungs
Usual threshold for production of cyanosis
Reduced hemoglobin formed by deoxidation of blood as it passes through the tissue capillaries (D)
Hemoglobin passing in reduced form from veins to arteries through aerated parts of the lungs (1=0.05)

FIG. 18. DIAGRAM SHOWING INFLUENCE ON THE MEAN CAPILLARY OXYGEN UNSATURATION (C) OF SIMULTANEOUS VARIATIONS IN D AND α

different regions of the body. (See, for example, the local effect of cooling the arm observed by Meakins and Davies.) If, however, a shunt is present and a certain fraction of the venous blood passes unaerated into the arterial stream, the unsaturation of the combined

venous blood in the right heart, resulting from the average D value of the entire capillary system, exerts an influence on the arterial unsaturation and thereby on C. With constant metabolism, the average D is inversely proportional to the minute volume output of the heart. In exercise, as previously mentioned, the blood flow does not increase in the same proportion as the oxygen consumption, so that D normally increases with local functional activity. The effect of simultaneous variations in α and D on C is shown in figure 18, in the same manner that the effects of l and T were shown in figure 17.

From figure 18 it is evident that, with normal pulmonary oxygenation ($l=0.05$) and normal hemoglobin content, the variability with varying α indicated in the following table exists in respect to the size of D required to raise C to the usual cyanotic threshold.

α	CAPILLARY OXYGEN CONSUMPTION, D, RESULTING IN C OF 6.5 VOLUMES PER CENT
	volume per cent oxygen
0.0	11.0
0.1	9.0
0.2	7.4
0.3	6.0
0.4	4.8
0.5	3.7
0.6	2.8
0.7	2.0

The influence of α in magnifying the effect of D on C is one of the reasons for the readiness with which cyanosis develops or increases, during exercise, in a patient with an unaerated shunt.

Since D depends on the ratio of blood flow rate to oxygen consumption rate in the capillaries, retarded circulation would have the same effect as increased oxygen consumption (exercise) in increasing D. If this effect is magnified by the presence of an unaerated channel admitting venous blood into the arterial, a slight retardation of the minute output of the heart (slight decompensation) might cause cyanosis in a patient with an unaerated shunt, whereas no cyanosis would ensue in an individual without a shunt.

It is further evident that if α is great enough ($\alpha = 0.38$), even the usual oxygen consumption ($D = 5$) causes a C exceeding the usual

cyanotic threshold of 6.5 volumes per cent unsaturation. Hence there occurs the intense cyanosis observed in children with congenital perforate septum and right to left shunt. In such cases there is usually also a polycythemia, so that the lT effect discussed above is added to the αD effect.

Finally, it is to be noted that since, with other factors normal, about 38 per cent of the venous blood must be shunted through an unaerated channel into the arteries before the cyanotic threshold of C is reached, if by a more rapid circulation D is lowered, α may be still higher without causing a C above the threshold. Consequently, absence of cyanosis in a resting patient does not exclude the possibility that a large fraction of his blood is passing through parts of the lungs to which no oxygen has access, or through other unaerated channels from the venous to the arterial system.

In the above consideration of the combined effects of D and α, D is considered to be the mean difference between arterial and venous oxygen contents, as expressed by the bloods in the arteries and right heart. Locally increased D values would, as shown in figure 15, affect the average unsaturation of the total blood, and C, only to the extent that they increase the reduced hemoglobin content of the combined venous bloods in the right heart.

If therapeutic means are applied which may simultaneously affect more than one of the three factors, l, T, and D, that can be varied in a given case (α being presumably constant in an individual over a short period of time), and cyanosis disappears or diminishes, it may not be possible to draw conclusions as to the main, original cause of the cyanosis. If oxygen therapy alone causes its disappearance, the main cause may be assumed to have been inefficient oxygenation in the lungs (high l). If digitalis causes the color to become normal, the cause of cyanosis may have been either retarded circulatory rate (high D value), or it may have been pulmonary embarrassment (high l value), since, as before mentioned, decompensated cardiacs show decreased lung volumes and oxygenation may be deficient. If venesection (lowering the hemoglobin content, T) or oxygen therapy (lowering l) is used together with digitalis, the interpretation of a disappearance of cyanosis is still more uncertain.

CLINICAL CONDITIONS ASSOCIATED WITH CYANOSIS

We shall in the following pages discuss the available data, indicating which factors are active in the production of cyanosis in the more important diseases in which it is encountered. Our present knowledge is so incomplete in most cases that it is only of suggestive value. There are a few conditions, however, in which the blood oxygen has been sufficiently studied, or the clinical condition so carefully analyzed, or both procedures have been so combined, as to indicate at least the probability concerning which of the contributory factors are responsible for the cyanosis. And perhaps discussion of conditions in which there is no satisfactory information may be of value in indicating problems that are urgently awaiting solution by exact study.

A. Diseases of the lungs and the air passages

A. Tracheal and bronchial stenosis. In patients suffering from stenosis of the trachea (foreign bodies, edema of the glottis, croup, etc.) cyanosis is a common and usually extremely marked symptom. No analyses of blood are available in such cases. The whole acute nature and dangerous character of these conditions makes it unlikely that such information can be easily obtained. It is, however, clear that decreased oxidation in the lung (increased l) is mainly, if not exclusively, responsible for the cyanosis in these cases. No other factor is likely to be involved in the production of the increased unsaturation of the capillary blood. Similarly, any large abnormality in the state of the modifying factors may be excluded. In these cases carbon dioxide retention adds its effect to that of anoxemia in causing the distress of the patient and producing the symptoms of suffocation.

In cases of bronchial stenosis cyanosis is not always observed. The acting factor here is a positive α, part of the lung being unaerated, although blood (α part of the whole) still flows through it. As we have estimated above, the value of the fraction α may reach about one-third before cyanosis appears. This means that about two-thirds of one lung may be shut off from aeration without appreciable cyanosis if l, T, and D are unchanged and the modifying factors normal. Oxygen therapy cannot relieve patients with tracheal and bronchial stenosis if the obstruction is total.

A series of experiments by Loewy and von Schrötter on the minute volume in man is interesting in this respect. By blocking a bronchus they cut a certain part of the lung off from aeration while the circulation was not hampered. They found that in normal individuals two-thirds of one lung (the right upper and middle lobe of the right lung) could be shut off from aeration without occurrence of cyanosis. When one whole lung was cut off cyanosis ensued. Some of their experiments lasted more than half an hour.

Table showing determinations of arterial oxygen unsaturation before and after obstruction of the air passage to one lung in animals (after Le Blanc)

SPECIES	OXYGEN CONTENT OF ARTERIAL BLOOD IN VOLUMES PER CENT		α ESTIMATED VALUE* OF FRACTION OF BLOOD PASSING LUNG TO WHICH AIR HAS HAD NO ACCESS
	Before obstruction of main bronchus to one lung	After obstruction of bronchus	
Rabbit	13.63	9.81	0.43
Rabbit	14.55	8.70	0.54
Rabbit	13.33	8.88	0.47
Rabbit	13.18	7.66	0.52
Rabbit	10.42	7.66	0.36
Cat	16.25	12.41	0.43
Cat	15.94	11.18	0.49
Dog	17.16	10.73	0.56
Goat	13.99	10.42	0.41

* Calculated by us from equation (4) (page 29) under the assumption that $D = 5$ volumes per cent and $l = 0.05$.

Our calculation that, with other factors normal, about one-third of the venous blood ordinarily must be shunted without aeration into the arteries in order to produce cyanosis, is in conformity with the results of these experiments, if we can assume that the normal fraction of blood passes through a part of the lung made inaccessible to aeration by bronchial obstruction. Hess (1912) and Le Blanc (1922) showed this to be the case in animals observed under similar conditions. Hess found that bronchial obstruction in rabbits had the calculated effect on arterial oxygen unsaturation, if the calculation was based on the assumption that the normal fraction of blood passed the lung after bronchial obstruction. Le Blanc, in 1922, obtained the results

tabulated above, and drew from his experiment the conclusion that obstruction of a bronchus does not markedly change the proportion of blood flowing through the right and left lung, respectively. We have, by applying our equation (4) for the calculation of α, and by assuming normal figures for D and l, estimated the fraction of blood passing the lung excluded from aeration. The figures show that from 36 to 56 per cent of the blood has traversed the obstructed side. No statements were made as to the side on which the operation was performed. The experiments, therefore, give no information regarding a possible difference in blood flow between the right and left lung.

B. Bronchitis. Bronchitis in adults is as a rule associated with cyanosis only if it is combined with other diseases such as emphysema and heart disease. Bronchitis may, as mentioned under the description of these conditions, then be an assisting factor in raising the capillary oxygen unsaturation to a point great enough to cause cyanosis. Bronchitis in children and babies is often associated with marked cyanosis. This may be due to the fact that the bronchitis in such cases usually is a bronchiolitis obstructing the air passages, as indicated at the post-mortem examination by the presence of atelectases of the lung tissue. It is, therefore, justifiable to assume that in such cases an increased arterial unsaturation exists, caused by shunting of small fractions of blood through unaerated parts; or, so to speak, by the additive effect of several α's. Concerning the modifying factors nothing is known, but it seems fair to assume that they play a minor part.

C. Emphysema pulmonum. "Cyanosis of an extreme grade is more common in emphysema than in other affections with the exception of congenital heart-disease. It is one of the few diseases in which a patient may be able to go about and walk into the hospital or consulting-room with a lividity of startling intensity." (Osler and McCrae, 1920.) It is, furthermore, characteristic that cyanosis in emphysematic patients increases markedly in exercise. Our information about the respiratory and circulatory disturbances in emphysema is still so incomplete that an exact physiological explanation cannot be given. That incomplete pulmonary reoxygenation of the blood is mainly responsible for cyanosis, seems probable in view of the well established pathological condition of the lung volumes (Siebeck; Lundsgaard and

Schierbeck), and the common complication with bronchitis in these cases. No analyses of the arterial blood are at hand to elucidate this question. In one patient, Lundsgaard and Möller (1922) found that the cutaneous blood was 96 per cent saturated, but no cyanosis was present in this case. Whether a hypothetically decreased reoxygenation of the blood in the lungs is due to increased l or positive α we do not know. M. Krogh did not find any decreased diffusion in three cases of emphysema, but none of these cases was reported to be cyanotic. That increased D, on account of slow circulation, plays an important part in producing cyanosis in emphysema, except in cases with heart failure, seems unlikely. Of the modifying factors little is known. It is a clinical experience that the superficial veins often are distended, especially in advanced cases (increased venous pressure?). To what extent this increases the width and the number of the blood-filled capillaries is not known.

D. Asthma bronchiale. Attacks of bronchial asthma are usually associated with a marked degree of cyanosis. The physiological pathology of this condition is unknown. However, clinical observations and what little we know about the changes of the lung functions (increased residual air, decreased vital capacity, prolonged and difficult expiration) point to incomplete pulmonary oxygenation (increased l) as the main factor involved. Direct evidence from oxygen analyses of arterial blood is still lacking. Increased D is probably seldom a significant factor. Distension of the veins, which is often seen during the attacks, may increase the importance of one of the modifying factors (the capillary distension). In asthma, as well as in emphysema, a diffuse bronchitis may add its influence to the other factors. In many cases the secretion in the air tubes may perhaps even be the main factor in diminishing the oxygenation of the blood during its passage through the lungs.

E. Pneumonia. Cyanosis is an important symptom in pneumonia patients. It is usually ascribed to respiratory disturbances. The following will show that in the main this is justified. By some clinicians, however, it is still looked upon as indicative of circulatory failure and treated accordingly. In spite of a number of studies of the condition, including some in which observations have been made

on the blood gases, we are yet uncertain concerning the main factor in preventing the reoxygenation of the blood in the lungs.

Hürter analyzed, in 1912, the arterial blood in two cases of pneumonia. He found in one case a saturation of 85 per cent; in another case, 78.6 per cent unsaturation (respectively, 2.74 and 3.29 volumes per cent). In the first case the left and right lower lobes were involved; in the last case, the right lower lobe was affected, and possibly the middle and upper also. He did not state whether or not cyanosis was present. If we assume that l and D are both normal (0.05 and 5.0, respectively), and attribute the cyanosis entirely to a fraction of blood passing unaerated (consolidated) parts of the lungs, we calculate that in the first patient the fraction was 0.27, and in the second 0.33. That would mean that about one-third of the blood perfused the unaerated parts, which in the first case comprised about 0.4, and in the second, between 0.2 and 0.5 per cent of the total lung tissue. This proportion of the venous blood can, as previously shown, enter the arteries unaerated without causing cyanosis. However, as we shall indicate later, it is not probable that arterial oxygen unsaturation in pneumonic patients is exclusively or even mainly due to an anatomical shunt.

Stadie's analysis of the oxygen content of the arterial blood in 33 patients with influenzal pneumonia (including 6 of the lobar type) (1919), and in 8 patients with lobar pneumonia (1922), shows that insufficient oxygenation of the blood is the most important cause of cyanosis in this condition. Increase in the oxygen consumption, D, was not often observed. The average value of D in Stadie's cases (1919) was normal. Le Blanc examined the blood gases in 6 patients with lobar pneumonia, 2 of whom showed slight cyanosis. In 1 patient (no. 20) with a slight cyanosis of the lips, ears, nails, and mucous membranes, he found an arterial oxygen unsaturation of 2.78 volumes per cent and a venous unsaturation of 6.69 volumes per cent. Calculated from these figures, the mean capillary oxygen unsaturation would be 4.73 volumes per cent, or slightly below what was found by Lundsgaard as the usual lower level. In another patient (no. 24) acrocyanosis was present with an arterial unsaturation of 1.92 volumes per cent and a venous unsaturation of 4.53 volumes per cent,

which gives a mean capillary oxygen unsaturation of only 3.22 volumes per cent. It must be remembered, however, that venous blood drawn from the cubital vein may differ considerably from venous blood from the acrocyanotic region. It is not at all improbable that peripheral disturbances in the circulation are mainly responsible for cyanosis in this last case. So far, however, no studies have been undertaken to investigate the condition of the capillaries in such cases, and their relation to cyanosis. A certain tendency to icterus exists and this may interfere with the shade of the color produced. Whether or not the heliotrope coloration in these cases can be ascribed to a mixture of ordinary cyanotic color and icteric color, we do not know; but the fact that a heliotrope variation of the cyanotic color has so far not been reported in, for instance, cardiac patients with cyanosis, points against this conception. The possibility that the heliotrope color could be caused by the presence of methemoglobin can probably be excluded because neither Abrahams, Hallows, and French, nor Stadie (a) could find any evidence of methemoglobin in the blood in their cases.

Whereas it seems proved that the main source of cyanosis in pneumonia is insufficient oxygenation in the lungs, it is still uncertain whether this is to be attributed to an increased l, that is to an insufficient oxygenation of blood passing aerated lung tissue, or to a positive α, that is to a fraction of blood passing consolidated, unaerated lung tissue. Most facts, however, seem to point to the first explanation, namely, that an increased l is the main factor. The disappearance of cyanosis after oxygen administration in these cases (Means and Barach; Barach and Woodwell; and Stadie, b) is evidence against a positive α. Furthermore, the extensive consolidation found without cyanosis in Stadie's (b) cases, nos. 1, 2, and 6, and the dry, bloodless condition of the consolidated parts of the lung in the stage of gray hepatization make it appear that the blood flow through the affected part is either prevented or much diminished, so that it is not likely to approach the necessary fraction ($\alpha = \frac{1}{3}$) of the total blood flow required to cause cyanosis. Kline and Winternitz showed that by injecting the lungs of rabbits and of man with Berlin blue through the pulmonic artery, only a very scanty color was produced in the consolidated region, whereas the normal parts were deeply stained; and by means of x-ray examinations of human lungs injected with a

Fig. 19. X-Ray Photograph of Pneumonic Lung (Pneumonia Lobaris Lobi Super. et Med.) Injected with Barium Sulphate Gelatine through the Pulmonary Artery. The Upper Lobe Shows Fewer Vessels than Are Normally Found. In the Middle Lobe only the Largest Branches Are Injected. The Shadow of the Lower Lobe Is More Dense and Massive than Usual, Suggesting a Compensatory Dilatation of the Vessels in the Non-Consolidated Area (after Gross)

barium emulsion Gross found that the pulmonic vessels in the regions of gray hepatization were almost completely impassable for the injected matter (fig. 19). This obstruction to the blood flow in the stage of gray hepatization is usually ascribed to pressure from the intra-alveolar exudate. Kline and Winternitz, however, have found some evidence pointing, as they believe, to multiple capillary fibrinogenous plugs (thrombi) in the pneumonic vessels as the cause. It is in this respect interesting that it has been shown (H. C. Gram) that in influenzal pneumonia (at the height of the disease) a very marked decrease in the blood platelets occurs. In twelve patients examined by Gram, the average number of blood platelets was 174,000 instead of 400,000 normally present. The highest observed value was 308,000, the lowest 46,000. In several of the patients a tendency towards hemorrhage was present. It seems possible, therefore, that the reason why the circulation is not cut off in the affected region of the lungs in patients with influenzal pneumonia, might be due to a diminished tendency of the blood to clot on account of platelet deficiency. The question is of theoretical and practical importance in many respects and needs further investigation.

Stadie reports one case (no. 2) with consolidation of the entire lower lobe, and entirely normal arterial oxygen (95 per cent of complete saturation) without oxygen therapy. Similarly, Le Blanc finds normal arterial oxygen saturation (98.1 per cent) in a patient with gray hepatization of part of the left lower lobe. It is, therefore, probable that the cyanosis is at least not mainly due to a shunt of blood through consolidated parts of the lungs in pneumonia. Whether it is due to shallow breathing (as suggested by Meakins, a and b), or to layers of fluid in alveoli (Hoover), or to decreased diffusion due to toxic injury to the alveoli (pneumonosis, Brauer), not filled with solid or fluid matter, we cannot decide.

Cyanosis was found to be a much more common and marked symptom in pneumonia patients during the influenza epidemics than in ordinary lobar pneumonia. This may be explained in part by the fact that the anatomical processes in influenzal pneumonia are different from those in ordinary lobar, and are such as to permit a large blood flow through unventilated pulmonary tissue. Influenzal pneumonia is usually of the bronchopneumonic type. On section,

the cut surfaces of such lungs were found to be red in color, and very rich in blood. Although one cannot with certainty draw conclusions as to the rate of perfusion from the amount of blood in the lung tissue, the appearance at least indicates that the blood flow was not prevented in the affected parts, as it probably is more or less prevented in lobar pneumonia. Apparently, anatomical conditions in influenzal pneumonia favor the production of a positive α to a larger extent than do those in lobar pneumonia. On the other hand, clinical observations have been made (Brauer) of cyanosis in such patients at a very early stage of the disease, before any anatomical lung lesion could be detected. In such cases an increased l would presumably be present. These observations led Brauer, as previously mentioned, to introduce the term pneumonosis.

F. Edema of the lungs. The mechanism causing cyanosis in edema of the lungs in man is not known. It is, however, probable as suggested by Hoover, that the accumulation of fluid along the epithelial walls of the lungs decreases the diffusion constant of oxygen. The same explanation is given by Barcroft for cyanosis in war gas poisoning, where edema was frequently observed. Oxygen therapy has been applied with success in many cases of edema of the lungs. Schjerning has produced lung edema in cats and dogs by intravenous injection of chloramine and subcutaneous injection of urethane, and also by chlorine inhalation. He found incomplete oxygenation of the arterial blood in these cases. In 2 cases (dogs 9 and 13) the anatomical changes in the lungs after chlorine inhalation were so slight that he assumes a functional disturbance of the epithelium (pneumonosis) as the cause of the marked increase in the arterial oxygen unsaturation.

It is, therefore, justifiable to assume that the main factor in producing cyanosis in patients with lung edema is increased l and that oxygen therapy consequently has effect in such cases. In some gassed patients an increased T has been observed (Barcroft and his associates) which may augment the influence of l, as previously discussed. In cases of heart failure with lung edema, a slow circulation may, through increased D, add its effect to the increased l. As to the modifying factors nothing is known. In heart conditions a distension of the peripheral capillaries may be present. Otherwise, the modifying factors seem to play a small part.

G. Pneumothorax and pleural effusion (collapsed and compressed lung). Acute (open) pneumothorax is usually associated with cyanosis, which in such a case is produced in the same manner as when the air passages to one lung are blocked, viz., by blood flow through unaerated lung space (positive α). Experimental evidence for this has been given by Sackur, who produced collapse of one lung by open pneumothorax in 5 rabbits and 1 dog. He determined the oxygen content in the arterial blood before and after the operation, and obtained the results given in the table. Assuming that the oxidation in the lungs was normal ($l = 0.05$) we can calculate T as $\frac{100}{95}$ times the oxygen content of the arterial blood before the operation. If the oxygen consumption, D, is 5 volumes per cent, we can estimate α from the equation

$$\alpha = \frac{A - l\,T}{V - l\,T}$$

Oxygen content in arterial blood before and after artificial pneumothorax (collapse of one lung) (after Sackur)

EXPERIMENT NUMBER	OXYGEN CONTENT IN ARTERIAL BLOOD IN VOLUMES PER CENT		ESTIMATED VALUE* OF α FRACTION OF BLOOD PASSING COLLAPSED LUNG	REMARKS
	Before pneumothorax	After pneumothorax		
14	13.6	7.3	0.56	Rabbit, right lung
15	15.3	11.2	0.45	Rabbit, left lung
16	12.3	7.2	0.50	Rabbit, right lung
17	14.3	7.6	0.57	Rabbit, right lung
18	14.4	11.0	0.40	Rabbit, left lung
19	21.5	15.8	0.53	Dog, left lung

* α is calculated by us from equation (4) (page 29) under the assumption that $D = 5$ and $l = 0.05$.

The results which are given in the table show that the estimated fraction of blood passing the collapsed lung is 50, 56, and 57 per cent in the 3 cases, where the right lung was collapsed, and 40, 45, and 53 per cent in the 3 cases (2 rabbits, 1 dog) where the left was collapsed. No definite change took place in the carbon dioxide content of the arterial blood, which in some cases was moderately increased, in others diminished.

If the lung tissue is abnormal, as for instance, in tuberculosis, cyanosis does not often ensue when spontaneous pneumothorax takes place. The reason for this is presumably that α cannot reach a value large enough to cause cyanosis on account of thrombosed vessels so often seen in tuberculous lungs.

In cases where the lung is not only collapsed, but compressed, either by effusion or by artificial (closed) pneumothorax, cyanosis is usually not observed. The reason for this is that in some cases aeration of the lung still takes place to a certain extent; in other cases that the blood flow through the compressed lung is either diminished or prevented by pressure in the pleural sac approaching or exceeding that in the pulmonary artery. In the case observed by Lundsgaard and Möller (b) this latter condition was evidently present. In 4 experiments on animals (rabbit, cat, and goat), Le Blanc found that the arterial oxygen unsaturation increased only slightly after a closed pneumothorax. If no aeration had taken place in the collapsed (compressed) lung, this would indicate that it had been passed by only a small fraction of blood. However, in 2 of his 4 experiments (nos. 1 and 4) some aeration must, as Le Blanc remarks himself, have taken place. In the first instance (experiment 1) he found that an obstruction of the main bronchus after pneumothorax increased the oxygen unsaturation of the arterial blood. After pneumothorax alone, the saturation of the arterial blood was 10.73 volumes per cent. However, when bronchial obstruction was added to pneumothorax, the saturation of the arterial blood went down to 9.16 volumes per cent. This shows that the ventilation of the (right) lung was not entirely prevented by pneumothorax itself. In the second instance, experiment 4, the arterial oxygen unsaturation went up when the amount of air (nitrogen) in the pleura was increased from 750 to 1,100 c.c. In 7 patients with tuberculosis, where the result of the x-ray examination seemed to exclude any lung function of the affected side, Le Blanc found the saturation of the arterial blood to be within normal limits before and after pneumothorax in all instances except possibly in patient no. 2. He (page 59), therefore, concluded that almost no blood had passed the affected lung. Attention should, at this place, be called to Bruns' six (animal) experiments on the content of blood in collapsed or compressed lungs. He found at autopsy that the amount of blood in a

compressed lung was smaller than that in the other lung and that it decreased with the degree of the compression. Further experiments on animals with simultaneous analyses of oxygen content of arterial and venous blood, and observations of intrapleural pressure, would be desirable. If venous blood from the pulmonary artery could be obtained, and if aeration of the compressed lung could be prevented, the fraction of blood (α) passing this lung could be calculated from our formula (4) under the assumption that the oxygenation of the blood in the non-compressed lung was normal (normal *l*).

B. Heart diseases

In circulatory disturbances cyanosis is a common symptom. It may occur early in the disease, as is often seen in lesions of mitral and particularly of congenital origin. In such cases it is usually associated with respiratory impairment (dyspnea) and is often seen only after exercise. Or, it may be a late symptom associated with definite signs of marked absolute heart insufficiency (stasis and edema). It may, therefore, be encountered in all kinds of advanced heart disease. Our present knowledge of the mechanism of the undoubtedly very complicated circulatory and respiratory disturbances in heart diseases is still so imperfect that it seems impossible to enter successfully into an analysis of the quantitative relationship of the different factors (causative and modifying) which participate in the production of cyanosis. Only suggestions can be made.

A. Congenital heart diseases. We shall not enter into the morphology of the congenital heart lesions. The possibility of the presence of a shunt and its direction as judged from postmortem examination is discussed in several papers of Abbott and her associates. From these papers valuable information about the relation of cyanosis to the varying morphological types may also be obtained. Readers are also referred to Peacock's, Keith's, and Mönckeberg's publications on the morphology of congenital heart lesions. In the very heterogeneous group of heart lesions which includes what are usually called the congenital heart diseases, cyanosis is, as mentioned, often an early and, as indicated by the name "morbus cæruleus," a very prominent symptom. It is, however, not so common as is often believed. Thomson found it only in 53 per cent of 136 cases and

Still describes it in 34 of his 100 observed cases. It is usually, since de Senac (1749), ascribed to a shunt permitting blood to pass unaerated from the veins to the arteries (positive α), although other explanations have been given (stasis, capillary malformations, and polycythemia). These factors include what we have termed *causative* and *modifying* factors, and all may perhaps enter into the formation in these cases. As to the possibility of a positive α in cases of congenital heart disease with cyanosis, we know that an abnormal communication between the right and left side of the heart is encountered in open foramen ovale in defective ventricular septum and in open ductus Botalli. Only in cases of complete fusion of the two ventricles into one, with resulting mixture of the two blood streams, is such a defect in itself sufficient cause for a positive α. In other cases the blood will flow *from left to right* unless, as first pointed out by Corvisart (1818), certain other abnormalities (as for instance pulmonary stenosis) are present, which might increase the pressure in the right ventricle above that in the left or in the aorta. Abbott, in Osler and McCrae's "Modern medicine," 1915, page 359, points out that a dilatation of the pulmonary artery with hypoplasia of the aorta is the rule in uncomplicated cases of widely patent foramen ovale or in large defects of the interauricular septum, and that the same condition exists, though in a lesser degree, in those rare cases of interventricular septal defect uncomplicated by pulmonary stenosis or dextroposition of the aorta. This furnishes, as Abbott points out, anatomical evidence that a considerable amount of blood must have passed from left to right through the abnormal communication. Figure 20 represents the circulatory conditions in a patient when a certain fraction of the blood passes through an abnormal communication from the left to the right side of the circulation. This diagram is constructed on the same basis as figures 12 to 15. In most cases of defective ventricular septum or persistent ductus Botalli, a pulmonary stenosis is present, but whether or not it is sufficient to produce the inversion of the pressure is difficult to decide.

In some cases a mitral lesion, a myocardial insufficiency, or a lung lesion resulting in an increased pressure on the right side of the heart might be the cause of the reversion of the shunt. (Cf. Bard and Curtillet's "Forme tardive de cyanose.") Interesting in this respect

is Carey's report on the clinical and pathological findings in two patients with defective interventricular septum of the heart, one with, the other without cyanosis. One began to show cyanosis at 6 years of age and died from septic endocarditis at the age of 25. Autopsy showed a communication between the right and left ventricle 1.5 cm. in diameter. A marked stenosis of the pulmonic artery was present, and the walls of the right ventricle equaled in thickness

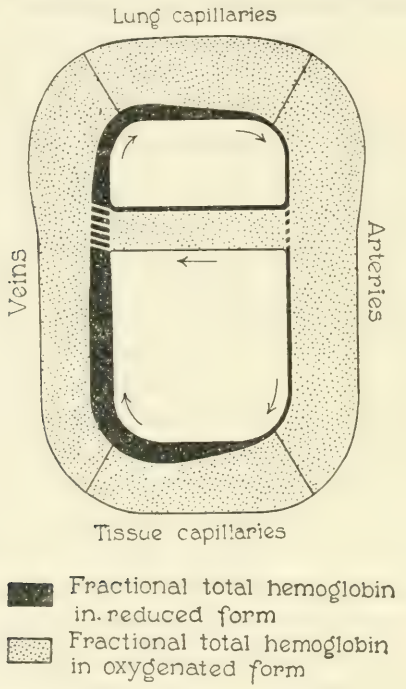

FIG. 20. DIAGRAM SHOWING THE PROPORTION OF OXYHEMOGLOBIN TO REDUCED HEMOGLOBIN IN DIFFERENT PARTS OF THE CIRCULATORY SYSTEM IN A CASE WHERE A FRACTION OF BLOOD PASSES FROM THE LEFT SIDE OF THE HEART TO THE RIGHT SIDE THROUGH AN ABNORMAL COMMUNICATION

the walls of the left. In this case conditions for a right to left shunt great enough to cause cyanosis were presumably present. The absence of cyanosis from birth to the sixth year can be explained in two ways: either by the presence of a left to right shunt during that period, which, of course, would not give rise to increased capillary

unsaturation; or by the passage of an amount of blood from right to left too small to give a capillary unsaturation above the threshold value. In the sixth year one must assume that for some reason or other the shunt had either become reversed, or the α had increased enough to cause cyanosis. The other case was a patient who died at the age of 35 years of mitral insufficiency. At autopsy an interventricular communication of 0.4 cm. in diameter was found. No pulmonic stenosis was present nor any hypertrophy of the walls of the right ventricle. We are justified in assuming that no blood can have been shunted from right to left in this case.

If, in a given case, we can assume that the oxygenation in the lungs is normal ($l = 0.05$), demonstration of an increased unsaturation A of the arterial blood is decisive for the presence of a positive α. If, furthermore, we could determine the oxygen consumption, D, and the hemoglobin content, T, we could estimate quantitatively the size of the fraction. Such data are, however, not available; in fact, the available information is not even quite sufficient to demonstrate qualitatively the presence of an unaerated shunt of venous blood into the arteries. Several valuable investigations concerning the circulation in such cases of congenital heart failure have been published. Plesch determined in 1909 the blood flow in a patient with persistent ductus Botalli, and obtained results which indicated a shunt from left to right. Hürter determined in 1912 the arterial unsaturation in a case of persistent ductus Botalli. At rest, the arterial blood was almost normally saturated, 91 per cent, giving an unsaturation of 1.8 volumes per cent (T was 20.35 volumes per cent). Hürter did not mention any abnormality of the skin color when the patient was at rest, so it is probably justifiable to assume that no cyanosis was present. "Es tritt aber schon bei geringen körperlichen Anstrengungen eine deutliche Cyanose mit Kurzatmigkeit auf." No analysis of the blood was made after exercise. Whether a certain fraction of the blood was shunted through the ductus from the right heart to the aorta during exercise on account of change in the pressure conditions cannot be decided, but at rest no blood could probably have been shunted. Boothby and Abbott proposed in 1916 to differentiate between a left to right and a right to left shunt in patients with congenital heart disease by determining the carbon dioxide tension

(instead of the oxygen tension as done by Plesch) in the arterial and venous blood. In left to right shunt the difference between the arterial and venous carbon dioxide is presumably smaller than in normal individuals, while the opposite is true in a right to left shunt. No determinations where this procedure has been used are published. Hess and Pearce in 1917 estimated the carbon dioxide tension in blood entering and leaving the lungs and obtained results which pointed to an unaerated shunt from right to left. Lindhard (b) made in 1913 a series of determinations of the minute volume in a patient where the postmortem examination, two years later, showed a defect of ventricular septum and a pulmonary stenosis. His results are of great interest, but not absolutely decisive to prove the existence of a positive α. Combined with analyses of the arterial blood, his observations would have made a most complete investigation of the circulation in such a case.

However, in most of the cases of congenital cyanosis, a positive α is presumably present. Other factors of which even less is known may be active in such cases. An increased l may add its effect to that of α, particularly, in later stages where lung involvement may be found. In such cases the influence of l would be magnified by the abnormally high hemoglobin content, T, commonly observed in such cases. The influence of T in magnifying the influence of a large l is shown in equation (9) and discussed on page 33. Also the modifying factors may be changed so that their influence is increased with resulting depression of the threshold of cyanosis or increase of the degree of the color present. Carpenter, in 1890, called attention to an increase in the width and number of capillaries and also to probable formation of new ones. Experiments on animals point in the same direction (Loeb), and Knapp showed in 1861 the increased width and tortuous shape of the capillary vessels in the retina. An increase in the blood volume in such cases has been shown by Bock and Means.

If, in heart failure, slow circulation develops, then increased oxygen consumption per unit of blood flow (increased D) may enter into the group of factors contributing to cyanosis. The effect of D will, as previously shown in equation (9), and discussed on page 36, be magnified by the presence of a positive α. Stasis would, furthermore,

act by increasing at least one of the modifying factors favoring cyanosis, namely, the volume of blood per unit of skin area.

It has been previously mentioned that equation (4) can be used for calculation of α in a given case of right to left shunt.[9] In man such a calculation can be only approximate because when α is positive, l cannot be determined experimentally. By animal experiments, however, it might be possible to throw light on the problem of the mechanism of the circulation in abnormal communication between right and left side of the heart. If a perforation of the ventricular septum could be produced and increasing constriction applied to the pulmonary artery, analyses of oxygen content of arterial blood and of blood from the two ventricles would enable us to calculate α with certainty.

B. Mitral lesions. The common occurrence of cyanosis in mitral and some forms of myocardiac lesions is probably related to the early involvement of the lungs through the increased pressure in the pulmonary circulation. It is therefore natural to ascribe cyanosis mainly to incomplete reoxygenation in the lungs. This viewpoint is sustained by Harrop's determinations of the oxygen in the arterial blood in 4 cases of myocarditis and 2 cases of mitral lesion. He found a moderate increase of the arterial unsaturation in all of them.

[9] The formula which would apply to a left to right shunt is developed as follows:
Let

A = oxygen unsaturation of arterial blood.
V_1 = oxygen unsaturation of venous blood in pulmonic artery after the admixture has taken place.
V = oxygen unsaturation of venous blood before admixture has taken place, that is, for instance, in the right auricle.
D = amount of oxygen taken away from the blood in the tissue capillaries.
β = fraction of blood passing from left to right through short circuit.

$$V_1 = V(1 - \beta) + \beta A \tag{1}$$

or

$$\beta = \frac{V_1 - V}{A - V}$$

therefore

$$\beta = \frac{V_1 - (D + A)}{-D} \tag{2}$$

or

$$\beta = 1 - \frac{V_1 - A}{D} \tag{3}$$

Whether this was due to increased l or to a positive α cannot be decided. The probability that increased l is responsible is indicated by the result of oxygen therapy in a series of cases (Barach and Woodwell, a). They found that administration of oxygen relieved the cyanosis and increased the arterial and venous oxygen saturation. It has previously been pointed out (page 26) that determination of the total blood flow (Means and Newburgh; Lundsgaard, 1916, a and b) and of the local blood flow (G. N. Stewart; Hewlett) also suggests that decreased flow rate may add to the cyanosis by increasing D.

Stasis may add its influence to the lung involvement not only by increasing D, but also, as previously discussed (page 14), by increasing the width and number of blood-filled capillaries, thus augmenting the most important modifying factor. No quantitative figures are, as mentioned, available for estimating the influence of this factor.

C. Aortic lesions. Aortic lesions, including hypertrophy of the left ventricle in patients with hypertension, are rarely associated with cyanosis before advanced stages, when the heart insufficiency is marked. The reason for this is probably that the lungs are usually not often involved during the first stages. Consequently, it appears that in aortic lesions, l and α, the two most powerful factors (see fig. 16) do not come into play at the early stages. For a decreased minute output of the heart alone to cause a cyanosis, through an increased D, the drop in minute output must be great (see fig. 18), unless the effect is reenforced by an abnormal distribution of blood through the action of the vasomotor mechanism, or by that of modifying factors (stasis). In a case of aortic insufficiency with marked decompensation, Hürter found that the arterial blood was only 85 per cent saturated (oxygen unsaturation 2.75 volumes per cent). Assuming normal D of 5.0, this would give a mean capillary unsaturation of $\frac{2.75 + 7.75}{2} = 5.25$ volumes per cent. This is in accordance with the observation that "auffallend war die geringe Cyanose." Harrop examined the blood oxygen in 2 patients (nos. 8 and 9) with aortic insufficiency. Both were slightly decompensated (edema). The lungs were clear in no. 9, and a few crackles were heard at the bases of no. 8. Neither of them was cyanotic. The arterial blood was normally saturated with oxygen (93 to 98 per cent) and the arterial oxygen

unsaturation was from 0.37 to 1.43 volumes per cent. *D* was somewhat increased in both cases, pointing towards a diminished blood flow. In aortic diseases, therefore, cyanosis is usually first encountered in the advanced stages, where lung involvements (and probably increased *l*) may be present.

D. Arrhythmia. There seems now to be sufficient clinical and experimental evidence to support the view first advanced by Wenckebach, Mackenzie, and Thomas Lewis, that an arrhythmic heart condition in itself may cause in some instances diminished output of the heart. This must necessarily result in a slow circulation, and consequently, in an increased *D*. Whether or not the cyanotic attacks observed in such patients can be solely ascribed to such increased *D*, is not known. It is, however, most likely that other factors are in play. An anatomical shunt (positive α) can be excluded. That a slow circulation in itself should cause a diminished reoxidation in the lungs is a priori very unlikely. Barcroft, Bock, and Roughton who examined the arterial blood of a patient with paroxysmal tachycardia found an increase in the degree of oxygenation in the lungs. Meakins (d), who examined 5 patients with auricular fibrillation, did not find any decrease in the oxygen content of the arterial blood except in cases with edema of the lungs. Similarly, Meakins found normal oxygen content of the arterial blood in 4 dogs with experimental tachycardia. H. G. Stewart examined patients before and after they had recovered from fibrillation with the assistance of quinidine therapy. He found arterial unsaturation within normal limits both before and after recovery. In the majority of cases of arrhythmic heart action showing cyanosis, valvular lesions and acute or chronic lung involvements exist, which, as shown by Meakins (d), may influence the pulmonary oxygenation of the blood. The valuable effect of oxygen therapy in 2 such cases was demonstrated by Meakins (d).

C. Cyanosis in patients under general anesthesia

It seems justifiable to ascribe the not infrequent occurrence of marked cyanosis in patients under general anesthesia to decreased reoxygenation of the blood in the lungs (increased *l*) on account of low oxygen tension. The fact that the cyanotic color disappears quickly after removal of the mask, and that cyanosis usually does

not occur when the open drop method is used, points also to this explanation. The flushed skin of anesthetized patients, particularly if ether is used, indicates also that the modifying factors may play an appreciable part. A study of the skin capillaries (the vasomotor mechanism) of patients under general anesthesia would be of considerable interest in this respect as in several other respects. As to cyanosis occurring in patients with the so-called delayed chloroform poisoning, nothing is known. In view of the fact that chloroform is a distinct protoplasmic poison, it seems possible that a functional disturbance of the lung epithelium might also be present in such cases. It would be of interest to study the effect of chloroform on the permeability of the lung epithelium to oxygen and carbon dioxide.

D. Cyanosis in intrauterine life and in the new-born

The question might naturally arise whether or not the mechanism of the embryonic circulation, with its physiologic admixture of venous and arterial blood does not cause cyanosis. It has been (Fouquier) considered a serious obstacle to de Senac's theory that "le fœtus n'est pas cyanosé, quoique les deux sang soient mélangés chez lui." Nothing is, so far as we are aware, known about the natural skin color of the fœtus, but in view of the high value of α necessary to cause an appreciable blue color, it does not seem very likely that a physiologic intrauterine cyanosis exists, at any rate not in the later stages of intrauterine life.

During normal delivery, an intense cyanosis of short duration due to deficient oxygenation might be considered a natural sequence of the change from placental to pulmonary oxygenation of blood which normally takes only a very short time.

In new-born children cyanosis is rarely observed. If it is present, it is probably always a pathological condition although it is supposed that some time (a few days) is required before the circulation adapts itself to the extrauterine life by closing the ductus Botalli entirely (see Bryce). However, even if some blood should be short circuited for some time after birth, cyanosis would probably not occur unless about one-third passed the shunt. Absence of cyanosis shortly after birth does therefore not disprove de Senac's theory. Hayem states that the cutaneous blood is darker during the first days after birth

than later.[10] No gas analyses or remarks about skin color are given by Hayem.

If abnormalities take place at birth, conditions are different; cyanosis is then very easily produced and may reach a very intense degree. It occurs under several pathologic conditions and is especially often seen in prematurely born children. The conditions in such cases are, of course, very favorable for the production of cyanosis. A delayed or impaired lung function may cause increased arterial oxygen unsaturation not only directly by incomplete oxygenation (increased l) but also indirectly by a delay in closing the ductus Botalli. Furthermore, the physiologic polycythemia in the new-born may magnify the effect of increased l. Our information about these conditions is so incomplete that a further discussion seems useless for the time being.[11] If clinical observation was focussed on these problems and combined with determinations of blood gases in such cases, information could possibly be gained which would at least be of great theoretical interest. Studies of the blood gases in the new-born face severe obstacles which, however, might be overcome by changing the usual technique for drawing blood. Venous blood might be obtained from the sinuses of the skull and samples of cutaneous blood might be used for the information usually obtained by analyses of arterial blood (Lundsgaard and Möller, 1922). The effect of oxygen therapy might prove of great value in deciding whether the cyanosis in such cases is mostly due to impaired lung function (increased l) or to a shunt (positive α). About the influence of the modifying factors (filling of capillaries, etc.) in these cases nothing is known.

[10] A sa sortie des capillaires cutanés, il est noir, presque à l'égal du sang veineux, et cette couleur, très accusée chez l'enfant n'ayant encore fait qu'un petit nombre d'inspirations, s'atténue un peu au bout de quelques heures, mais elle persiste pendant les premiers jours de la vie jusqu' à une époque encore indéterminée. Elle est encore plus noirâtre que celle du sang de l'adulte, douze jours après la naissance (Hayem, p. 179).

[11] H. Bakwin has determined, in a number of babies (some prematurely born), the oxygen in venous blood drawn from the sinuses of the skull, before and after oxygen treatment. It was found in several instances that the cyanosis disappeared and the oxygen content of the venous blood was increased after administration of oxygen. This indicates that the blue decoloration in these babies was due to insufficient oxidation of the blood in the lungs (decreased l) and not to a short circuit through the ductus Botalli or through the lungs. No determinations of the oxygen in the arterial blood were made (personal communication added to proof).

E. Polycythemia vera (Vaquez-Osler's disease)

The first observed case of this disease was described by Vaquez in 1892, but "en l'absence de toute autre hypothèse plausible," Vaquez diagnosed it as a case of congenital heart disease with polycythemia and cyanosis, until the postmortem examination a year later disclosed the splenomegaly and the absence of any heart lesions. It so happened that cyanosis went down in the history as one of the cardinal symptoms of Vaquez-Osler's disease together with polycythemia and splenomegaly. Several authors, among them Osler himself, have been inclined to describe the color change in these cases not as a cyanosis, but as a "congestion or ruddiness" of the skin. It has therefore been proposed to term the skin color erythrosis instead of cyanosis (Paltauf).[12]

Hürter determined the arterial unsaturation in a case of polycythemia and found an unsaturation of 1.49 and 3.07 volumes per cent. The last figure is above normal and points towards an increased *l*. The increase in the arterial unsaturation is almost large enough to turn an erythrosis into a cyanosis, even if *D* and the modifying factors are normal. No observations of the skin color are reported by Hürter. Lundsgaard (d) determined the venous oxygen unsaturation in a similar case where the skin color was red. Of 4 determinations the highest value was 6.6, the lowest 5 volumes per cent. Assuming a normal *D*, the arterial blood was normally saturated in this case. However, even if the skin color in Vaquez's disease is red rather than blue, it must be admitted that such patients become very readily, either generally or locally, cyanosed. There appear to be two main reasons for this: the first being the increased hemoglobin content, *T*, which magnifies the influence on capillary unsaturation of *l*. This is discussed and shown in detail on page 33 and following. The second reason is the abnormal state of one of the modifying factors, namely, the condition of the capillaries, the number and width of which may be increased (see page 15). It has furthermore been shown that the state of the capillaries is highly variable, a condition which Thaysen has named capillary ataxia. Information on this is, how-

[12] In 1919 one of us (C. L.) proposed the term erythrosis for the skin color in Vaquez's disease, not knowing that Paltauf had already used this name.

ever, at present too slight to allow any estimate of the relative importance of these two factors in the production of cyanosis. Quantitative studies on the skin capillaries in such cases would be desirable, in combination with determination of the three factors l, T, and D involved in the production of capillary unsaturation in these cases.

F. Anemia

Clinical observations show, as pointed out by Lundsgaard (c), that anemic patients exhibit less tendency to become cyanotic than do normal individuals. This is explained in part by the decreased value of T in such cases (see page 33), in part by changes in the modifying factors due, as pointed out before, to decrease in the number and width of blood-filled capillaries per skin area unit (see page 16). If the hemoglobin content of the blood is less than 30 per cent normal (5 grams hemoglobin per 100 c.c. of blood), cyanosis does not usually appear. However, by applying prolonged stasis (tension below systolic pressure) to the arm of a patient with hemoglobin of 21 per cent, we were able to produce a faint trace of cyanotic color (non-published observation). This is due to the increased influence of the modifying factors which, as previously mentioned, may depress the threshold value of the mean capillary unsaturation at which cyanosis appears. Combined studies of the color changes of the skin following stasis applied under measured pressure, of the oxygen of the blood, and of the number and width of the capillaries, would be instructive. It seems better in such cases to compare the skin color of an arm after stasis with a normal individual than with the pale color of the opposite arm, and it must be remembered that the mean capillary unsaturation in prolonged stasis probably equals the venous unsaturation on account of the back pressure.

G. Cyanosis at high altitudes, mountain sickness

The factor mainly responsible for the production of cyanosis at high altitudes is incomplete oxygenation in the lungs (increased l) due to low atmospheric oxygen tension. Its effect, as pointed out before, may be magnified by the presence of a polycythemia (see page 34 and equation (9)). In normal individuals with $T = 20$ volumes

per cent, and $D = 5$ volumes per cent, one would expect to find that cyanosis would begin at an oxygen saturation of the arterial blood of about 80 to 85 per cent, which would give a mean capillary unsaturation of 6.5 and 5.5 volumes per cent, respectively. This expectation accords, as previously mentioned, with the experience of Barcroft and his party in the Andes. If air with a low partial pressure is inspired, the same effect is seen (Lundsgaard, c). The relief of cyanosis in such cases by breathing oxygen is due to return to normal of the increased unsaturation (l) of the pulmonary blood. We have previously discussed the influence of anemia in hindering the appearance of cyanosis in such cases because with less total hemoglobin (T) present, a given percentage unsaturation (l) produces a smaller concentration of reduced hemoglobin, and less blue color. Other factors being equal, of 2 individuals, 1 polycythemic, the other anemic, the former would show cyanosis at high altitudes more readily, but be nevertheless the better adapted to endure them.

H. Local cyanosis, acrocyanosis

Cyanosis is more often localized than general. The reason for this is that to factors acting generally on the capillary unsaturation (as increased l or positive α), there is added a locally increased D. Furthermore, the modifying factors are usually of more importance in one region than in another. Consequently, in cases of deficient oxygenation in the lungs, we frequently find that the cyanotic color is either confined to, or is most marked at certain places (hands, feet, nose, lips, cheeks, and ears).

In other cases the factors producing cyanosis are of purely local, peripheral nature, so that abnormal skin color naturally is confined to the parts where such factors act. An obvious example of locally produced cyanosis is caused by applying stasis to the arm, or by exposing an extremity to cold. Clinically, local cyanosis is especially often seen at the extremities, and is most marked at the distal parts. For this condition the word acrocyanosis is often used. Such cases are often observed, and the cyanotic color is usually ascribed to nervous influence, to thermic irritation, or to local stasis.

The factors acting in these cases must presumably be: first slow blood flow and consequently increased D, as already suggested by

Raynaud; second, an increase in the influence of two of the modifying factors, namely, the increase in number and width of blood-filled capillaries, and the shape of the capillary reduction curve (see fig. 11), which probably on account of back pressure and blocking of the blood flow would be very abnormal so that the average capillary unsaturation probably would be near V instead of $\frac{A+V}{2}$. Apart from the experiments reported by Lundsgaard (c) and by Meakins and Davies, no information is available as to the blood oxygen in such cases. A closer study would be desirable, but certain difficulties are encountered here. It seems impossible to be certain as to the area drained by the vein from which the blood is drawn. The cubital veins receive blood from the superficial layer of the entire forearm, and probably to a certain, and possibly varying, extent from the deeper tissues. Nothing is known about it. Analyses of blood from the more peripheral and smaller veins would be useful, but have not yet been done.[13] In a study of the oxygen content of the so-called capillary blood from incisions in the finger tip, Lundsgaard and Möller (b) found that blood so obtained was to be looked upon as arterial blood.

As to the influence of the modifying factors, it is, as mentioned, easy to demonstrate qualitatively that the visible skin capillaries of the fingers increase in number and width, and probably also in length, if artificial stasis with cyanosis of an arm is produced. No quantitative and almost no qualitative study has been made of the influence of different pressure levels on the number and width of the capillaries. Such studies combined with careful observation of the degree and distribution of the cyanotic skin color might prove valuable.

Slow blood flow in patients with Raynaud's disease and in other cases of acrocyanosis has been observed directly by capillaroscopy, and increased width and length of the capillaries have been observed (Weiss and Holland; Pribram and Henius; Halpert; Boas; see fig. 10).

[13] Goldschmidt and Light have found that the superficial blood from the back of the hand has a higher percentage saturation of oxygen than the blood drawn from the deeper veins at the elbow. Their study includes the effect of various factors upon the oxygen of these bloods. This work will be published in the near future (personal communication added to proof).

Boas has shown that the capillary circulation in acrocyanosis varied with the clinical condition of the patient. When the fingers were cyanotic and cold, he found a low capillary blood pressure and a sluggish streaming of blood. When the hands appeared normal, or when they were immersed in hot water and became erythrotic, the capillary pressure increased and the streaming became faster.

Bruns and König, and Carrier, have studied by capillaroscopy the influence of application of heat and cold on the skin capillaries in man. The ordinary sequence of events which takes place during a transition from a warm to a cold environment (air or water) is described by Carrier in a publication from Krogh's laboratory as follows: "When the surrounding atmosphere becomes more and more cold, the capillaries and arterioles, which in warmth are open and have an even, rapid stream become contracted. The flow of blood through them becomes very much reduced and the skin is white. Further cooling, however, paralyzes the capillaries so that they relax. For a time there is enough blood coming through the contracted arterioles to give a slow arterial stream in the capillaries; but, as the cold becomes more intense, the arterioles are so completely contracted that the flow of blood stops. The open capillaries fill with venous blood and the skin is cyanotic." It is clear that both the causative and modifying factors are involved in producing the cyanotic color of the type described by Carrier. So far we are unable to judge about the quantitative influence of the two factors in such cases. It seems probable that much information regarding the undoubtedly very marked influence of the modifying factors on the appearance and degree of acrocyanosis might be obtained by a further study of the influence of different stimuli (mechanical, thermic, electrical, and chemical) on the condition of the skin capillaries in cyanotic and non-cyanotic individuals.

HISTORIC DEVELOPMENT OF THEORIES OF CYANOSIS

Much clinical material on cyanosis has been published. More than 500 publications have appeared since the time of de Senac. Most of these are in casuistic form, but quite a few are monographs or dissertations. In most of the publications that have been accessible to us, the authors have, besides reporting their material, entered into dis-

cussion of the theories of cyanosis. These theories are of considerable interest for several reasons. First, because the two most important of them were created by de Senac and Morgagni, from the two first well observed cases. In spite of the fact that these two men observed only one case each,[14] they created from their observations theories which in the main still hold good when they are interpreted in the modern language. Second, because the variations in the conceptions of the cause of cyanosis are very intimately connected with the leading viewpoints in medical science as a whole.

In the following we shall very briefly give an account of the theories of cyanosis. We shall pay most attention to the historic background for these theories, less to the discussion pro and con. The theory holding an admixture of venous and arterial blood to be a cause of cyanosis will, however, be discussed in more detail. We have reserved the historical review for the conclusion of our paper in the belief that after the reader has read an exposition of the causes of cyanosis, as revealed by the methods of modern physiology, he may be in a better position to appreciate the mental keenness with which some of the early clinicians interpreted their observations.

As is known, de Senac (1749) was the first to advance a theory concerning the cause of cyanosis. He thought it was due to an admixture of venous and arterial blood through the heart. A few years later (1761) Morgagni suggested pulmonary stenosis as the cause. He thought that a stenotic condition of the valves caused stasis and cyanosis as well. Although the validity of de Senac's theory was supported by observations of cyanosis in patients in whom conditions for an admixture of venous and arterial blood were present, his theory was nevertheless repeatedly challenged because anatomical conditions for the admixture of venous and arterial blood were observed without the occurrence of cyanosis.

In 1823 Louis in a critical discussion of 20 cardiac cases, partly from

[14] de Senac reports a case of chronic cyanosis in a man, twenty-seven years of age, in whom at autopsy the two ventricles were found to be united into one. Morgagni's case is a girl, sixteen years of age, who had been cyanotic since birth. At autopsy, marked pulmonary stenosis and open foramen ovale was found. The condition of ductus Botalli is not mentioned.

the literature and partly observed by himself, reached the following conclusion (page 341):

"Il est donc impossible, soit qu'on s'appuie sur le raisonnement ou sur l'expérience, de soutenir que la couleur bleue soit un effet du mélange du sang noir et du sang rouge, d'autant plus que d'après ce qui a été dit, ce mélange paraît avoir lieu à un degré plus ou moins marqué dans tous les cas, et que néanmoins, au rapport des auteurs, et d'après les observations que nous avons citées, la couleur bleue est loin d'être constante et surtout générale (obs. IV). Ajoutons, comme le remarque M. le professeur Fouquier, à la suite de l'observation recueillie par M. Thibert, que la peau du foetus où ne circule que du sang noir, n'est pas bleuâtre.

"L'impossibilité d'expliquer la couleur bleue dans les cas dont il s'agit, par le mélange des deux espèces de sang, étant bien démontrée, il faut considérer les faits sous un autre point de vue. Morgagni nous semble avoir donné la véritable explication de celui qui nous occupe, dans le commentaire de l'observation que nous lui avons empruntée. Pour se rendre compte de la couleur livide dont il s'agit, il remarque que le rétrécissement de l'orifice de l'artère pulmonaire, par suite d'une ossification qu'il croit congénitale, devait causer un grand embarras dans la circulation du sang; que celui-ci restait en stagnation dans le ventricule droit, l'oreillette correspondante et par suite dans tout le système veineux, d'où résultait la couleur livide de la peau. Cette explication nous semble d'autant meilleure, qu'on ne saurait en donner une autre de la coloration bleue qu'on observe si souvent dans l'anévrisme des différentes cavités du cœur."

In 1824 Gintrac analyzed 53 cases of cyanosis from the literature. He found that in some instances conditions for admixture of venous and arterial blood occurred without cyanosis. He did not, however, consider this an obstacle to the adoption of de Senac's theory because, as stated first by Corvisart, certain abnormal pressure conditions, often caused by pulmonary stenosis or other obstacles to the circulation, usually must be associated with congenital malformations of the heart in order to force blood from the right ventricle to the left or from the pulmonic artery to the aorta through the ductus Botalli. A few cases of babies, where the aorta was found to come from both ventricles without causing any cyanotic color, he tried to explain by assuming that the venous and arterial blood differed less at birth than later.

Bouillaud, who in his article in "Dictionaire de médicine et de chir-

urgie pratiques" (1831) explains cyanosis entirely by admixture, admits later on (1835) that the objections, especially of Louis and others, are much against the mixture theory. He admits, furthermore, that admixture cannot explain the cyanosis in venous congestions (aneurisms of the heart). Still he thinks that admixture must be of importance (page 572); "Quant à nous, il nous paraît toujours probable que le mélange du sang noir avec le sang rouge peut contribuer à la production de la cyanose; mais ce mélange a lieu, peut-être, plus rarement qu'on ne l'avait cru jusqu'ici."

After exhaustive analysis of 80 cases of morbus cæruleus which at that time were available in the literature, Moreton Stillé (1844) reached the following conclusions (pages 30 to 41):

"1. That cyanosis may exist without admixture of venous with arterial blood. 2. That there is no proportion between cyanosis, and the degree to which the blood is mixed. 3. That complete admixture of the blood may take place without cyanosis. 4. That contraction of the pulmonary artery is present in every case of cyanosis. 5. That it never exists without the concurrence of cyanosis. 6. That it is an adequate explanation of the most important phenomena of the condition."

Breschet described a case with the left subclavian artery arising from the pulmonary vein and still no cyanosis of the left arm existed. For that reason he did not consider admixture of venous and arterial blood a cause of cyanosis. Niemeyer in his pathology also stated that (congenital) cyanosis is caused by stasis although he admitted that some other cause must be present (page 328):

"Dass die bedeutende Cyanose der Kranken mit angeborenen Herzfehlern einen besonderen Grund hat, ergiebt sich auch aus dem Umstand, dass Kranke mit angeborener Cyanose weit später hydropisch werden als Kranke mit aquirirter Cyanose. Hinge die Cyanose nur von der Stauung ab, so würde dies nicht der Fall sein."

Grisolle (page 416) makes the following remarks about the pathogenesis of cyanosis (in morbus cæruleus):

"Deux opinions ont été émises sur la cause de la coloration bleue, qui est un des phénomènes prédominants de la maladie. Corvisart, M. Gintrac, l'attribuent au mélange des deux sangs; Ferrus et M. Louis l'expliquent

plutôt par la gêne considérable de la circulation. Cette dernière opinion nous semble être la seule admissible. Pour réfuter la premiere, il nous suffra de dire qu'on a vu la cyanose manquer dans les cas où l'aorte naissait du ventricule droit, ou bien encore lorsque le cœur n'était constitué que par une oreillette et par un seul ventricule. Enfin, comme l'a remarqué fort judicieusement le professeur Fouquier, le fœtus n'est pas cyanosé, quoique les deux sangs soient mélangés chez lui. La couleur cyanique s'explique par la gêne de la circulation dépendant du vice primordial de conformation du cœur et des lésions qui l'accompagnent le plus souvent, comme le rétrécissement des orifices, la dilatation des cavités et l'hypertrophie des parois, lésions qui forcent le sang à stagner dans les capillaires de la peau."

These examples show that the fact that conditions for admixture of venous and arterial blood have been found without cyanosis has been one of the most serious objections to de Senac's theory of cyanosis.

That the concentration of reduced hemoglobin in the skin capillaries must *reach a certain grade* before visible cyanosis results, makes it understandable that the blue color is not always present, even when there is reason to believe that blood actually passes through the unaerated channels from the right heart to the side, present in patients with deficient ventricular septa or with patent ductus Botalli.

To de Senac and his followers for a hundred years the physiological facts were not available to make possible the conception of oxygen deficit or reduced hemoglobin in the blood as the cause of cyanosis. To them the venous and arterial blood meant two different species with a qualitative, essential difference, clearly expressed by Claude Bernard in a sentence in his lecture on the color of the blood (11th leçon, page 253):

"Cependant, nous pensons que cette distinction, fondée sur la coloration du sang, est loin d'être aussi absolue et d'avoir la signification qu'on a voulu lui donner, en supposant que le sang rouge est un sang doué de certaines propriétés et que le sang noir est doué de propriétés toutes différentes."

In view of the vague conception of the difference between arterial and venous blood, and of the absence of a tradition of quantitative thinking, it is readily conceivable that qualitative evidence carried weight

against de Senac's theory. The existence of cases in which no cyanosis was seen in spite of the fact that the anatomical conditions were present for admixture of venous blood to arterial seemed conclusive against it. That the admixture of a certain *proportion* of venous blood with arterial would be required to cause cyanosis did not enter into contemporary reasoning.

Any causative connection between the blood gases and the cyanotic color could, of course, not develop before it was shown that oxygen and carbon dioxide were present in the blood. It was not until 1837 that Magnus proved even the existence of the blood gases. The importance of this discovery is best elucidated by quoting Magnus (page 188):

"On avait jusqu'à présent préféré admettre que l'acide carbonique se formait dans les poumons plutôt que par l'action des vaisseaux capillaires, parce que l'on n'avait pas encore démontré sa présence dans le sang; à cela se joignait une altération chimique qu'il éprouvait dans les poumons, son changement de couleur. Et cependant c'est un fait bien connu que le sang devient plus foncé en absorbant de l'acide carbonique. Ce changement de couleur pouvait donc s'expliquer par le dégagement de ce gaz. . . . . Certainement, en le purgeant de son acide carbonique, le sang ne devint jamais d'un rouge aussi clair que le sang artériel; mais il paraît d'ailleurs que l'absorption de divers gaz y produit des colorations diverses. . . . . Il est donc vraisemblable que le sang artériel doit sa couleur rouge à ce qu'il s'y trouve moins d'acide carbonique et à l'absorption de l'oxigène."

The qualitative difference between the venous and arterial blood as to the blood gases was first clearly given in 1859 by Claude Bernard (page 290, 13th leçon) who defines venous blood as follows; "en quoi consiste la vénosité: c'est une propriété en vertu de laquelle le sang a changé de couleur et est devenu plus capable d'absorber l'oxygène." It is natural that the cyanotic color in the following period was attributed not to the venous blood in general but to abnormalities in the blood gases. Through analyses of the blood in suffocation the "Venenblut in höchster Potenz" (see Zuntz, 1882, p. 42), a decrease in oxygen and increase in carbon dioxide were found. In local stasis with cyanosis and in cyanotic heart patients (Kraus, 1897, pp. 20 and 36) an increase in the carbon dioxide content of the blood was

found. It seems, therefore, natural that discussion might arise as to which of these abnormalities cyanosis should be ascribed, although physiologists, have definitely shown that the color change of the blood is due, not to alterations in the content of the carbon dioxide, but to changes in the oxygen saturation of the hemoglobin.

Another factor, the importance of the increased number of red blood corpuscles, entered into the discussion of the cause of cyanosis after Toennissen's discovery of polycythemia in heart disease (1881), and particularly since Krehl's observations of marked polycythemia in a patient with morbus cælureus (deficient ventricular septum) in 1889, and Vaquez's description (1892) of a patient with polycythemia vera and cyanosis. This factor was considered, at any rate, mainly responsible for the cyanosis in several of these cases. Some confusion has been introduced because the difference between the red color usually present in polycythemia (erythrosis) and the blue cyanotic color was not clearly defined.

It has been pointed out in this paper that an increased hemoglobin concentration causes a given fall in arterial oxygen tension to produce a greater concentration of reduced hemoglobin, and thereby causes more intense cyanosis.

Morgagni's theory proposing stasis as the cause of cyanosis has played an important part. That stasis is one of the remote secondary causes of cyanosis is very easily demonstrated. Furthermore, stasis and cyanosis are often united in the same patient, particularly in cardiac disease. Cyanosis in other conditions, such as emphysema, asthma, and pneumonia, is difficult to explain by stasis; but even in such conditions the other possible factors have been neglected, with an influence on therapy which cannot in all cases have been helpful.

This short historical sketch is sufficient to show that what we have considered the *cause* of cyanosis; the oxygen unsaturation of the capillary blood, corresponds fairly well to de Senac's theory of the importance of admixture of venous and arterial blood. Similarly, what we have termed the main *modifying factor*, the filling of the capillary bed, is in the main covered by Morgagni's theory that cyanosis is produced by peripheral stasis. The magnifying effect of the hemoglobin concentration in the blood on inefficient oxygenation in the lung capillaries gives the physiologic explanation of the impor-

tance of the increased number of red blood corpuscles of polycythemia in the production of cyanosis. And the modifying factors cover the idea that new formation of capillaries played a rôle in the production of the color in cyanotic patients. Each of these theories of the past contains, so far as we are able to see, a part of the truth, and none of them contains the whole truth.

The different factors, causative and modifying, entering into the production of cyanosis, are in a given case of different quantitative importance. A full analysis of the bedside observation is not always possible, but for the understanding of the observation and the treatment of the patient it is of importance to carry the analysis in every single case as far back as possible to the physiologic and morphologic components of the condition.

SUMMARY

On the basis of Lundsgaard's demonstration that the cause of cyanosis is an abnormally large amount of reduced hemoglobin in the capillary blood, the quantitative effects of four factors contributing to this cause have been estimated, viz., (1) the total hemoglobin content, (2) the degree of oxygen unsaturation of the arterial blood coming from aerated lung areas, (3) the proportion of blood passing from right heart to left through unaerated channels, and (4) the oxygen consumption in the capillaries.

There are various other factors which modify the coloration. Such are local skin vascularity, pigmentation, thickness of epidermis; and also the fact that the mean capillary content of reduced hemoglobin, $\frac{1}{2}(A + V)$, only approximately represents the average content. With changing conditions the latter may, instead of being midway between venous and arterial, approximate either more nearly than the other. The effect of these modifying factors is to cause the mean capillary concentration of reduced hemoglobin at which cyanosis becomes perceptible to vary from 4 to 6 grams of reduced hemoglobin per 100 c.c. of blood, and perhaps sometimes even more widely, although it appears usually to lie near 5.

The main clinical conditions in which cyanosis is a symptom have been considered in connection with the causative and modifying factors present, and attempts have been made to estimate the functional and anatomical significance of the cyanosis in these conditions.

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THE ETIOLOGY OF NEPHRITIS

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INTRODUCTION

Writers have from time to time objected to the use of the term nephritis to designate the bilateral, non-suppurative affection of the kidneys first set apart as a clinical entity by Richard Bright. The grounds for such objection originate in the belief that many of the conditions included under this heading are primarily not inflammatory but that they are either degenerative or atrophic. Classifications embodying these ideas have accordingly been proposed. But the new classifications are, on the whole, no more satisfactory than the older one, since in the first place it is far from proved that either degeneration or atrophy is more important than inflammation in the pathogenesis of any of these affections; and in the second place, these newer classifications are no more etiological than the older one. The old clinical terms, acute, subacute and chronic nephritis, have been and still are very useful because they call to the mind of the physician a picture with which he is familiar; and offer him, even if not a sure footing, nevertheless the safest point of departure for his search into the cause or causes of the disease.

Acute nephritis is typified by its sudden onset; by the scanty, high colored, often bloody urine containing much albumin and many casts; by generalized edema; and by a variety of disturbances of the digestive tract and central nervous system brought together under the heading of uremia.

Chronic nephritis, in contrast, generally comes on slowly and insidiously. The cases may often be separated into two subgroups: the chronic glomerulonephritis of the pathologists and the so-called arteriosclerotic or vascular nephritis. The former generally affects young adults. Two-thirds of Bell and Hartzell's (1) 37 cases occurred in the third and fourth decade, the average age of Ophuls (2) 19 cases was thirty-nine years. These patient's show a marked tendency towards the development of severe anemia. Generalized edema is common. The specific gravity of the urine is often normal or high. Marked albuminuria and an abundant sediment containing many casts is the rule. Uremia usually closes the picture.

Vascular nephritis is a modern synonym for the affection which the older clinicians had in mind when they made the diagnosis, chronic interstitial nephritis. This form of renal disease makes its appearance in older adults. Edema is uncommon and when it does occur is due to heart failure. The urine is pale, of low specific gravity and contains only a small amount of albumin and a few casts. Anemia is rare. Death is more often due to vascular accidents or heart failure than to primary renal failure.

Hypertension and cardiac enlargement are commonly present in both types of chronic nephritis.

It is frequently impossible to decide in individual cases, whether one is dealing with chronic golmerulonephritis or vascular nephritis. For this reason many clinicians prefer, for the present, to place all the chronic cases in one group. Anyone who has compared the clinical diagnosis with the autopsy findings will appreciate the strength of their position. Still, from the point of view of etiology, there is something to be gained by the attempt to subdivide these chronic cases into two groups, for the chronic glomerulonephritis appears to bear a close etiological relationship to acute nephritis whereas the cause of vascular nephritis forms only one part of a large and difficult problem. The true relationship of nephritis to hypertension and arteriosclerosis is at present far from clear.

The term subacute nephritis is used as a convenient designation for all those cases which are neither typically acute nor chronic. In this sense its connotation is purely clinical and it frankly includes more than one group from the etiological point of view. The occa-

sional cases of acute nephritis which continue to show activity for an unusually long time may be placed in this group. But since their etiology is that of the original acute nephritis, they need no separate discussion. The term is most aptly applied to the renal disturbance found in individuals presenting continued albuminuria and cylindruria who can not recall an antecedent acute nephritis and who are often unaware of any renal abnormalities. On the other hand, absence of such signs as marked hypertension, cardiac enlargement, edema, and the demonstration of fairly normal kidney function, indicates that such patients do not belong in the group of chronic nephritis.

A third clinical type of renal disease seems to belong more properly under this heading than under that of chronic nephritis. I refer to the cases characterized by inveterate generalized edema of insidious onset accompanied by very great albuminuria. Hypertension and left ventricular hypertrophy are not found in at least the type examples. Older clinicians often referred to these cases as subacute or chronic parenchymatous nephritis. By others more especially the pathologists, this disease was spoken of as tubular nephritis to distinguish it from glomerulonephritis. Still later Friedrich Müller (3) proposed the term "nephrosis" for these cases in order to express his conviction that the essential lesion was a degeneration of tubular epithelium rather than an inflammatory process. Later writers, notably Vollard and Fahr (4), have dealt with this condition as an etiological entity. Whatever its true nature, it has gained sufficient prominence to entitle it to at least a special subheading.

Enough has been said to indicate that no classification at present in use is satisfactory. Clinically the distinction between acute and chronic renal disease can ordinarily be made but the physician is too often unable to go beyond this point. And yet there are well substantiated reasons for believing that there are several varieties of both acute and chronic renal affections. Is our difficulty not due to this, that kidney disease makes itself manifest largely through disturbed function and that these aberrations of function unfortunately do not arrange themselves in well defined groups, each characteristic of a single specific etiological factor?

ACUTE NEPHRITIS

It has been known for a long time that acute inflammation of the kidneys was a not uncommon complication of some acute infectious diseases. We find this idea expressed in the old term "scarlatinal nephritis," and medical teachers have for decades pointed out this latter affection of the kidneys as the type example of acute nephritis. But not until recently has it been realized what a place of overwhelming importance, acute infections and especially streptococcus infections, hold in the causation of acute nephritis. The following table recently published by Hill (5) as the result of his investigation of the

TABLE 1

DISEASE	NUMBER OF CASES
Tonsillitis	14
Unknown etiology	15
Scarlet fever	4
Impetigo contagiosa	4
Otitis media	4
Pneumonia	2
Tonsillectomy	2
Purpura	2
Carious teeth	2
Stomatitis	1
Cold	1
Total	51

cause of the acute nephritis in the cases admitted to the Children's Hospital, Boston, is very instructive in this respect.

Two-thirds of Hill's 51 cases immediately followed diseases which are thought to be varieties of streptococcus infection. Included in this group are tonsillitis, impetigo contagiosa, otitis media, tonsillectomy, purpura, carious teeth, stomatitis. Over half the cases occurred in children who were, at the time of entrance, or who had in the immediate past, been suffering from streptococcus infection. Hill is strongly of the opinion that many of the cases of unknown etiology, were secondary to mild throat infection. In addition to this, most pathologists would insist that the complications of scarlet fever, among which the inflammation of the kidneys would of course be included, are due to streptococcus infection.

Vollard and Fahr (4) as a result of their careful study of several hundred cases of Bright's disease occurring at all ages, are led to conclude that more than half of the cases of acute nephritis follow infection of the tonsils and upper respiratory tract. Their list of causes, slightly modified to meet the present needs, is as follows:

TABLE 2

DISEASE	NUMBER OF CASES	DISEASE	NUMBER OF CASES
Tonsillitis	37	Pneumonia, empyema	7
Scarlatina	21	Bronchitis, pleurisy, and tuberculosis	4
Infected wounds	11	Gastroenteritis	1
Erysipelas	2	Malaria	1
Infectious arthritis	5	Lead	3
Purpura	2	Pregnancy	7
Colds, otitis, etc.	19	Unknown	21
Total	97	Total	44

The streptococcus diseases have been placed in the left hand column; all other causes in the right hand column. Some of the cases in the latter column may be and probably are examples of streptococcus infection. How many of those listed as unknown had their origin in a streptococcus infection which gave rise to no symptoms?

Pathologists who have sought for the cause of the acute nephritis which they have found in their autopsy material, have also been impressed with the etiological importance of infection. Bell and Hartzell's (1) recent study in this field contains a table here reproduced (table 3) which shows the association between infections discovered at autopsy or in the clinic in the 32 examples of acute glomerulonephritis found by them in 3300 autopsies.

It should be pointed out that most of the "cases" of acute glomerulonephritis in this table were nothing more than complications of infection of other important organs. Bell and Hartzell state that in 9 of their 32 cases the involvement of the kidney was too slight to cause any prominent clinical findings and that in 12 others the renal disturbance was masked by associated disease. They have picked out only 11 from the group as typical clinical cases; but in 8 of these death appeared to be due to complicating infection rather

than to the nephritis. There were apparently only 3 cases in which the clinician thought that the main disease was acute nephritis. This difference in the selection of material on the part of Bell and Hartzell and of Vollard and Fahr and of Hill, no doubt accounts for the prominence of endocarditis in table 3. But this table, as well as the two preceding ones, emphasizes the importance of the streptococcus as a cause of acute renal lesions. Most, if not all, of the cases

TABLE 3

Infections found in 32 cases of glomerulonephritis

DISEASE	NUMBER
Vegetative endocarditis	12
Puerperal sepsis	1
Empyema	5
Peritonitis	3
Streptococcus bacteriemia	6
Pneumococcus bacteriemia	2
Septic sore throat	3
Erysipelas	3
Lobar pneumonia	2
Suppurative otitis media	1
Suppurative pharyngitis	1
Streptococcus arthritis	1
Infected surgical wound	1
Meningitis	1
Acute arthritis (not present at death)	4
Severe bronchitis	1
Variola	1
Tuberculosis with cavities	1
Ulcerative colitis	1
Diabetic gangrene	1
Purulent conjunctivitis	1
No localized infection	4

of vegetative endocarditis were caused by the streptococcus, and there were in addition 11 other cases in which the disease was due to the streptococcus. Hence more than two-thirds of these 32 cases of acute glomerulonephritis, occurred in persons who died of streptococcic disease.

In more than one-third of Bell and Hartzell's 32 cases, the main disease was vegetative endocarditis. Councilman (6) long ago pointed out the very frequent association between endocarditis and

acute glomerulonephritis. Acute, usually ulcerative, endocarditis was found by him in 10 of the 28 bodies whose kidneys showed acute nephritis. Much more recently Baehr (7) has made a special anatomical study of the renal lesions found in persons dying of subacute bacterial endocarditis. He points out that in most cases of endocarditis due to the Streptococcus viridans, a lesion of the glomerulus due to the plugging of one or more capillary loops by bacterial emboli, is found. The remainder of the involved glomerulus and the uninvolved glomeruli appear to be normal. These lesions usually cause no disturbance other than microscopic renal bleeding. But exceptionally when the emboli are very numerous symptoms resembling those of subacute hemorrhagic nephritis may occur and may even cause a fatal issue. If the cardiac lesion should go on to healing and if many glomeruli have in the meantime been plugged, a contracted kidney may ensue and produce the typical picture of chronic nephritis.

Billings (8) and his co-workers have familiarized us with the importance of searching for focal infections as a cause of nephritis. Such infections do not ordinarily cause enough subjective disturbance to make themselves known to the patient and hence are entirely overlooked when he is questioned concerning antecedent infections which might have caused his nephritis. These hidden nests of bacteria nearly always harbor streptococci and are most often found in the tonsils and teeth. Some of the cases of acute nephritis which in the past have been placed in the group of "cause unknown" were perhaps examples of the effect of focal infection upon the kidney.

One may expect the percentage of cases of acute nephritis demonstrated to be due to infection by the streptococcus to grow as our knowledge of bacteriology increases, but there will remain a few cases which are caused by the pneumococcus, the diphtheria bacillus and perhaps the staphylococcus. Whether the acute nephritis occasionally seen in tuberculosis is due to the action of the tubercle bacillus as stated in some textbooks, or is produced by the secondary invaders, cannot at present be answered.

How do the bacteria injure the kidney—by lodging and multiplying in the renal parenchyma? Or are the lesions caused by poisons elaborated by the bacteria at a distance and carried in the blood stream

to the kidney? All the evidence speaks in favor of the latter view. Cabot and Crabtree (9) cite a long list of observers who have shown that pathogenic bacteria of many sorts injected into the blood stream will pass through the kidney without harming it. Furthermore, histological examination of nephritic kidneys, fails to demonstrate either colonies of bacteria or localized collections of pus cells indicative of suppuration. The lesion, on the contrary, is typified by its diffuse character such as would be expected as the result of the action of a soluble toxin. A picture very closely resembling that seen in the human cases has been obtained by at least one investigator by means of the toxin of the diphtheria bacillus in the absence of the organism itself. Bailey (10) by injection of large doses of diphtheria toxin into rabbits produced a lesion of the glomerulus which consisted chiefly of necrosis and thrombosis of the capillaries of the tufts, accompanied by hemorrhage, formation of hyaline masses and invasion by leucocytes.

Occasionally, as the result of acute poisoning by one of the heavy metals, a clinical picture amply justifying the use of the term, acute nephritis, comes under the observation of the physician. But such cases, because of their totally different etiology and pathogenesis should not be included in the group of acute nephritis. Histologically these kidneys are characterized by extreme degeneration of the tubular epithelium. In the classic examples of corrosive sublimate poisoning, complete necrosis of the lining cells of the tubules is seen. The term "acute renal poisoning" would be a satisfactory etiological designation for such cases.

SUBACUTE NEPHRITIS

1.

Reference has already been made to that group of cases whose renal disease did not begin with an acute nephritis and whose clinical examination does not justify the diagnosis of chronic nephritis. Such individuals do not present the signs and symptoms of far advanced irreparable renal pathology. The blood pressure is not far from normal, the heart is slightly if at all enlarged; nitrogen retention, if present, is trifling; and the output of phenolsulphonephthalein

is not much delayed. But small amounts of albumin and a few casts are found week after week; and the patients often show slight edema—frequently in the form of puffiness of the face in the early morning—and lesser grades of anemia.

We have had the opportunity of observing an instructive case of this type in the Medical Clinic of the University Hospital.

Miss H. B. M. entered the clinic January 23, 1919, complaining of weakness, lassitude and edema. She was twenty-six years old. She had had measles, mumps, whooping cough and typhoid fever in childhood, but had never had scarlet fever or diphtheria. In 1913, she had a tonsillectomy performed to prevent the recurrence of attacks of sore throat with which she had been troubled for several years past, though she had never had a severe attack of tonsillitis. She has occasionally had a trifling sore throat since. In January, 1917, the patient was told that her face and eyes were swollen and she herself noticed swelling of the ankles at times. In April of the same year, a physician told her that she had Bright's disease. She was in bed under treatment for the next three months and then returned to work. She continued her occupation as stenographer until coming to this hospital, but feels that she has been slowly going down hill. The edema has not increased but she has been greatly hampered by weakness, eye strain and headaches. She has lost 25 pounds in weight. Physical examination the day after entrance revealed no abnormalities. It was noted that the tonsils appeared to be normal. The urine upon repeated examinations showed albumin and a few casts. The blood pressure was 130 mm. systolic and 90 mm. diastolic. The blood urea was 18 mgm. per 100 cc. and the phenolsulphonephthalein output 75 per cent in two hours. These functional renal tests indicated that the kidneys were hyperirritable and in conjunction with the history and urinary findings emphasized the necessity for searching for a focus of infection. This was discovered by special methods in the tonsils. Shortly thereafter while still under observation she had a sharp attack of tonsillitis. A few days after the subsidence of the attack, tonsillar enucleation was performed. About 1 drachm of pus was found behind each tonsil. She was then discharged and told to remain in bed for another two months. This she did and then returned to her work.

In September, 1919, about six months after the removal of the tonsils, she returned to the hospital at our request. She stated that she felt much improved and that she had gained some weight. Her urine on five examinations showed neither albumin nor casts. The blood urea was now normal—30 mgm. per 100 cc.—as was the phenolsulphonephthalein output which

amounted to 46 per cent in two hours. There seemed to be every reason for believing that the source of the renal irritation has been eliminated by the tonsillectomy and that the patient might consider herself cured.

The further history of the case, however, proved that our optimism was far from justified, for about six months later a sample of urine showed 5.5 grams of albumin per liter and a few hyaline casts. She reentered the clinic on April 12, 1920, and stated that she had been at work continuously since leaving the hospital six months previously. She had, however, noticed a tired feeling in her limbs and her feet had been slightly swollen in the morning. The physical examination at this time showed slight edema of the head of the optic nerve and retina, a heart which was not enlarged to percussion but by orthodiagram was found to be slightly enlarged, a normal blood pressure, normal blood urea and phenolsulphonephthalein output. The urine always showed albumin but never any casts.

What conclusions may we draw in regard to the relation between focal infection and nephritis from the course of this case? The removal of a focus of active infection was rapidly followed by the complete disappearance of every sign and symptom of renal disease. Evidently there had been some intimate connection between the tonsillar infection and the nephritic disturbance. But why did some signs of nephritis reappear after a period of apparent health following the tonsillectomy, if the tonsillar infection had been the source of the nephritis? One might argue that the "cure" was apparent but not real, that the long rest following tonsillectomy had taken sufficient load off the kidney so that the gross signs, albumin and casts, disappeared, but that the kidney, in fact already injured by the poisons of infection, was still undergoing an insidious sclerosis whose rate was perhaps somewhat diminished by the removal of the source of the toxins.

It is at present commonly held that cases of this type are caused by the poisonous products of focal infection. In order to establish such a supposition as a fact it is necessary to show that these patients are generally cured or greatly benefited by the removal of foci. It is not sufficient to demonstrate the presence of foci of infection in nephritis for this no more proves that the nephritis owes its origin to the infection than it does that the infection is a complication of nephritis. But evidence of the desired sort has not been published.

The eradication of foci of infection in patients coming to the University Hospital has thus far not resulted in a single cure.

2.

The cases characterized by massive persistent edema of insidious onset have, according to some writers, an etiology quite distinct from other forms of nephritis. Müller, some years ago, proposed the term "nephrosis" for these cases in order to indicate clearly what he believed to be the essential lesion. He pointed out that the histological picture was dominated by extreme degeneration of the tubular epithelium. Hence, argued Müller, it must be conceded that the use of the word nephritis which implies inflammation is not correct. Müller's suggestion was adopted and amplified by Vollard and Fahr (4). The condition as set down by them shows in addition to the edema of insidious onset, a urine of high gravity and small volume, containing large amounts of albumin and many casts but no blood. There is never hypertension nor cardiac hypertrophy. Retinal changes are absent. Nitrogen retention is trifling or absent but salt retention is marked. At autopsy one should find the large white kidney with or without amyloid. In their opinion the amyloid is an unimportant by-product. They had under observation 49 cases of which 13 were acute and all of which showed rapid recovery. The diagnosis was of necessity based solely on clinical findings, and one is prone to ask oneself how many of these 13 cases would have shown acute inflammatory lesions of the glomeruli in addition to tubular degeneration had the kidneys been examined histologically. Seven of the cases formed a complication of diphtheria; 3 occurred in pregnancy and 2 as a part of secondary lues. There were 33 chronic cases of which 15 complicated chronic tuberculosis, 5 lues and 3 occurred as a part of chronic suppuration. The reader can scarcely fail to recognize these chronic cases as examples of the old classic amyloid disease of the kidneys. There were in addition 7 cases of "genuine" nephrosis of unknown etiology.

At least 40 of Vollard and Fahr's 49 cases of nephrosis were clearly complications of some other disease, usually a chronic infection. From the point of view of etiology, "nephrosis" as described by Vollard and Fahr might be defined as an affection of the kidneys

characterized by degeneration of tubular epithelium and generalized edema, which occurs as a complication of tuberculosis, syphilis and chronic suppuration.

It is not known how such chronic infections injure the kidney. Vollard and Fahr suggest that this form of nephropathy is brought about by the action of abnormal metabolic products upon the tubular cells. They point out that analagous histological lesions have been repeatedly produced by injection of phosphorus, arsenic, uranium and other substances, in animals, but that in these animal experiments, the most important feature of the clinical picture—the edema—is lacking. Merely because certain metallic poisons will produce a histological picture which resembles what is seen in the renal tubules of certain individuals who succumb to chronic tuberculosis or some prolonged suppurative process, does not help the writer in his efforts to arrive at a conception of the nature of the substances which causes the "nephrosis" of chronic suppuration.

Epstein (11) has repeatedly called attention to certain chemical aberrations in the blood serum and dropsical fluids of persons presenting chronic edema and albuminuria. He has found very marked alterations in the protein content of the serum. Normally the blood serum contains 6 to 8 grams of protein to 100 cc., of which one-third is globulin. In Epstein's cases the total protein averaged less than 4 grams, of which the globulin formed about 90 per cent. Chronic nephritis and cardiac conditions studied by the same method showed normal values for albumin and globulin. Epstein cites the work of Diabella and von Ketly to prove that the reduction of the protein content of the serum is not due to dilution (hydremia) and further points out that the diminution cannot be due to migration of the proteins into the tissue spaces because his analyses show that the edema fluids are made up principally of salt and water with a trifling protein content. He lays great stress on another type of chemical change occurring in these cases. He has found a very great increase in the lipoid content of the blood. This increase in lipoids, according to him, is evidence of a metabolic disturbance similar to that occurring in the starvation of diabetes and in pellagra and is, at the very least, evidence of a grave nutritional disturbance.

In his earlier papers, Epstein referred to his cases as examples of chronic parenchymatous nephritis or nephrosis. Latterly he appears to believe that he is dealing with a primary endocrine disease, two of whose signs are chronic edema and albuminuria. The rather striking therapeutic results attributed to thyroid feeding, strongly incline him to the view that the kidneys are not chiefly responsible for the symptom complex studied by him.

Recently Kahn (12) has published his attempts to repeat Epstein's findings. He writes:

> In practice, that group of which Epstein speaks, seems to be very rare, of 16 cases of chronic parenchymatous nephritis with marked edema and of 7 with only slight edema, I have not found a single case which showed the marked protein and lipin deviations indicated by Epstein. . . . . Without going into pains-taking argumentation, it will be seen that there is no protein change in chronic parenchymatous nephritis which is characteristic of that disease and which does not occur in the other types of the nephritides and in other disease. The cases of so-called nephrosis which Epstein describes must be very rare and it is possible that he has culled the instances which he reports from an extremely large number of cases of chronic parenchymatous nephritis in which the albumin-globulin ratio in the serum is not markedly disturbed.

Since Kahn has not found the changes described by Epstein in typical cases of "chronic parenchymatous nephritis," and since Epstein himself has come to regard his cases as endocrine disturbances, there appears at present to be no adequate reason for classifying this condition as a disease of the kidney.

CHRONIC NEPHRITIS

The term chronic nephritis is applied to disease of the kidneys when the process is in the stage of sclerosis, atrophy and contraction, regardless of antecedent causes.

Out of the welter of conflicting literature amassed during the past half century in an attempt to explain the causation of chronic nephritis, two convictions stand out clearly. They are these, that some contracted kidneys are the end stage of an acute or subacute nephritis of bacterial origin; and that nearly all of the remaining cases are inti-

mately related to arteriosclerosis and cannot be properly understood unless the two processes, the sclerosis of the vessels and the sclerosis of the kidneys are studied together.

1.

We owe to the clinicians the idea that chronic nephritis is at times the direct outcome of an antecedent acute or subacute bacterial nephritis. The case reported by Mann (13) in 1895 and followed by him from its beginning in a typical acute scarlatinal nephritis, through various intermediate stages until finally the classic picture of chronic nephritis had developed, is here reproduced because it affords such clear-cut evidence of the bacterial origin of some cases of chronic nephritis.

Mann was called in the year 1866 to see a girl of fourteen with scarlet fever who shortly thereafter developed acute nephritis with dropsy. The acute features disappeared in a few weeks and the patient regained her health with the exception that albuminuria continued. During the next twenty-eight years, the urine was examined six or eight times a year and albumin was always found. For seven or eight years after the original attack the patient had occasional subacute attacks of nephritis with scanty smoky urine containing numerous casts. In the intervals the urine showed only an occasional cast. In some of the attacks there was considerable edema. The attacks usually followed exposure to cold, but sometimes no cause could be found. The attacks were entirely absent during the latter part of her life. With the exception of occasional attacks of "bronchial catarrh" and of "subacute rheumatism" the general health was good. From 1866 to 1880 the urine invariably contained albumin from 0.2 to 1 per cent. About 1880 she began to have polyuria with a low specific gravity. The amount eventually reached 60 to 80 ounces. Casts were now rare and red blood cells were never seen. A few weeks before death the quantity fell off, the blood pressure rose and the heart enlarged. Autopsy showed a large left ventricle. The kidneys were very small. The capsule could not be stripped. The surface was granular. Microscopically the interstitial tissue was much increased, especially in the pyramids. There was no recent cellular infiltration. The larger arteries were little altered but were surrounded by a large amount of adventitious tissue. The smaller arteries showed great thickening of their walls, especially of the intima which in exceptional instances was so thick as nearly to obliterate the

lumen. The glomeruli and Bowman's capsules were scarcely distinguishable owing to fibrous transformation. The tubules were dilated and atrophied. Mann says in conclusion "The pathological report places this case among those in which a process beginning as acute nephritis results in a condition which is indistinguishable from the common type of granular kidney. The resemblance is complete."

But the literature contains only a very few such cases, and students who have traced series of acute cases have shown that only an occasional one progressed to chronic nephritis. Vollard and Fahr (4) found that only 3 of their 71 acute cases, became chronic. Ernberg (15) located 40 of 106 adults who had had acute nephritis before the age of fifteen years and found normal urine in all. In 16 of 50 adults who had had acute nephritis between the ages of fifteen and thirty years he found normal urines in all but 4, 2 of whom had recently developed renal disease which was not related to the original acute attack. It is apparently very unusual for the acute nephritis of childhood to develop into a contracted kidney.

When acute nephritis occurs in adults it seems to show a somewhat greater tendency to become chronic but the available information is so meager that no satisfactory conclusion can be drawn from it.

Pathologists, in the attempt to trace chronic glomerulo-nephritis back to its source, have been more impressed with the etiological importance of acute nephritis than have the clinicians. Thus Loehlein (16) stated on the basis of certain histological details that chronic glomerulonephritis was very commonly the sequel of an acute nephritis. Bell and Hartzell (1) picked out four from their 37 cases of chronic glomerulonephritis which apparently developed from acute nephritis.

This important question can be answered finally only by systematic reëxamination of several hundred cases of frank acute nephritis (adults as well as children) over a period of ten years or more.

Even though it is possible to account for only a small minority of the cases of chronic nephritis as sequels of infections that first made themselves manifest in the form of acute nephritis, still many observers believe that much or even most chronic nephritis is a product of infection. It is assumed that infections usually in themselves too trivial to attract the patient's notice, are capable of elaborating

poisons whose slow hidden action finally comes to light in the form of a sclerosed and atrophied kidney. Billings (8) for example, states that chronic nephritis due to focal infection is very common. This assertion is based on the frequent association between infected foci and chronic nephritis. But such evidence does not convince. How is one to decide whether the infection is a complication of the nephritis, a cause of the nephritis, or whether the association of the infected focus and the nephritis in the same individual is greater than would be expected from the laws of chance when dealing with two such common conditions?

Pathologists as well as clinicians have endeavored to discover the relationship between infection and chronic nephritis. In so doing they have picked out a group of cases whose nephritis they attribute to the action of bacteria, and are prone to use the appellation "chronic glomerulonephritis" when speaking of these cases. They see in the glomeruli of such kidneys the signs of inflammation. The lesions are for the most part so far advanced as to have lost all or nearly all cellular detail. Most of the injured glomeruli have been converted into firmly contracted scars whose past history is not revealed by the microscope. But careful search will disclose an occasional leucocyte in these scarred glomeruli. In other glomeruli not so completely cicatrized, the remains of a crescent may be seen. One or two glomeruli in which a cellular exudate fills Bowman's space may be found. These signs of inflammation form a strong connecting link between this type of chronic nephritis and acute glomerulonephritis which is almost certainly bacterial in origin. The belief that chronic glomerulonephritis is due to infection is further strengthened by the evidence obtained from the study of subacute cases. Here all stages from an acute glomerulitis to completely sclerosed glomeruli may be seen. The most recent publication in this field is by Bell and Hartzell (1) who as part of their discussion of the etiology of chronic glomerulonephritis have summarized the data from their own 29 postmortem cases. In 16 of this group no history of infection was obtained and no old infections were found at necropsy. Four cases apparently followed acute nephritis, leaving a total of 9 out of 29 in which antecedent infection could be established either by history or examination. Usually the evidence of infection was

obtained from the history, the patients having stated that they had had either tonsillitis or scarlet fever years before. Bell and Hartzell point out that the high incidence of tonsillitis and scarlet fever in persons who do not develop nephritis, detracts from the value of these data; and that the evidence of associated (streptococcic) infections is not at all satisfactory in the chronic group. But they are nevertheless convinced by what they see in these kidneys with the microscope that the lesion is produced by infection. They write "The histological evidence is convincing that the glomerular lesions in the chronic kidneys are the healing stages of acute lesions, and if one admits that acute glomerulitis is due to infection it is difficult to escape the conclusion that chronic glomerulonephritis is due to the same cause."

From the laboratory we have direct evidence that nephritis may be produced by the presence of virulent organisms in the body. Pernice and Scagliosi (17) years ago showed that the subcutaneous or intravenous injection of pathogenic bacteria into animals would cause an acute exudative glomerulitis. The animals were not allowed to live long enough to develop chronic lesions.

Klotz (14) injected cultures of organisms isolated from the blood of patients suffering from infectious "heart disease." The best results were obtained in those animals that received inoculations of the same organism at long intervals. He was able to trace the course of the disease from the acute nephritis in animals that lived only a few days through subacute stages in animals that lived longer, up to granular kidneys.

The accumulated evidence appears to indicate that the chronic nephritis of younger adults is a product of infection. The average age of Bell and Hartzell's cases was thirty-seven years and two-thirds of them fall in the third and fourth decades.

It remains to account for the chronic nephritis of older adults. Among the 3300 consecutive autopsies performed by Bell and Hartzell there were, according to their criteria, 29 examples of chronic glomerulonephritis and 26 cases of arteriosclerotic or vascular nephritis.

The intimate association between arteriosclerosis and the contracted kidney was emphasized as long ago as 1872 by Gull and Sutton (18)

when they wrote "There is a disease in which the arterioles throughout the body are altered, which constitutes a general morbid change of which contraction and atrophy of the kidneys is part and parcel." Johnson (19) who antedated Gull and Sutton had called attention to the abnormal state of the arteries in nephritis. His work gave rise to the idea that nephritic hypertension caused hypertrophy of the media and that the thickened media later degenerated and finally presented the picture of atheroma. Such a process was manifestly a result and not a cause of the contracted kidney. Gull and Sutton, on the contrary, insisted that the vascular disease was the primary lesion and that the contracted kidney was a result thereof.

Ziegler accepted the conclusion of Gull and Sutton and added the idea that there are two types of kidney disease caused by arteriosclerosis. He spoke of a form in which there was a widespread atheroma of the large arteries of the body including the kidney and in which the kidney showed large scars scattered through an otherwise fairly normal parenchyma. Furthermore the clinical picture was that of generalized arteriosclerosis rather than that of renal insufficiency. The condition was contrasted with what he called the primary or genuine contracted kidney. Here a severe arteriosclerosis of the smaller vessels of the kidney (and of some other organs) with less marked involvement of the large somatic vessels, was said to have caused a diffuse renal atrophy with secondary connective tissue replacement. The disease of the kidney, in this latter form, domiated the picture and other disturbances were secondary to it.

The study of the relation of arteriosclerosis to nephritis was taken up at this place by Jores (20). He was able to show by means of a special technique that the vascular lesions found in the contracted kidney were those of true arteriosclerosis and that analagous arterial disease was regularly present in the small vessels of some other organs. He concluded that the vascular lesions occurring in the kidneys were one part of a widespread true arteriosclerotic process which always antedated the nephritis. He explained the pathogenesis of the lesion by the statement that arteriosclerosis of the afferent arterioles (vasa afferentia) of the glomeruli, by gradually cutting off the blood supply to the glomeruli, gave rise to a slow progressive atrophy of the organ. One encounters some difficulties when one analyzes Jores conclusions.

In the first place, Loehlein and other observers have pointed out the almost constant occurrence of identical lesions in the so-called secondary contracted kidneys, that is, the variety believed to be the end stage of a glomerulonephritis due to bacteria. What relation does the sclerosis of the kidney bear to the arteriosclerosis in these secondary contracted kidneys and what is the relation between the arteriosclerosis and the infection? Are we to assume that here the vascular disease has been caused by the same poison as the nephritis? If so why are we not justified in further assuming that the hypothetical poison which caused the arteriosclerosis also caused the renal sclerosis in the case of the primary contracted kidney? In other words, that the two scleroses have a common etiology rather than that they stand in the relation of cause and effect to each other. In the second place, it is claimed by many that the arteriosclerosis of the secondary contracted kidney is an effect of the nephritis. If this is true, might we not reason by analogy that the arteriosclerosis found in the so-called primary contracted kidneys is also an effect and not a cause? The literature contains masterly defenses of each one of these hypotheses. The Germans, Aschoff, Herxheimer, Vollard and Fahr, accept as established beyond further question Jores' dictum that the primary contracted kidney is always caused by arteriosclerosis of the small renal arteries. They, for this reason, speak of this condition as a sclerosis or atrophy, to be thought of apart from the true nephritides which are inflammations of bacterial origin. But Vollard and Fahr evidently found considerable difficulty in making their clinical diagnosis of primary renal atrophy dovetail with the anatomical findings, for they felt obliged to postulate two clinical-morphological groups of renal sclerosis. The first they labelled "benign sclerosis" and stated that this form represented the cases of "essential" hypertension. The symptoms were said to be entirely of vascular origin; and the sclerosis of the kidney, even though far advanced, was said to cause no disturbance and to be of altogether secondary importance. The second form they called "malignant sclerosis" in order to indicate that here the renal insufficiency dominated the clinical picture. They speak of sclerosis to which a nephritis has been added by way of offering an explanation for the occurrence of renal symptoms. They, however, admit that

the "etiology of the nephritis is obscure," that it is not due to bacterial toxins; and that these malignant kidneys cannot be histologically distinguished from the "benign" ones. It is not necessary to reproduce their discussion intended to explain the differences in their two types of renal sclerosis. To the writer it appears as if they had made confusion worse confounded.

Ophuls (21) in 1912 published the results of a careful study of the kidneys in a thousand unselected autopsies. He reached several important conclusions. He found, in the first place, that he could not distinguish histologically or otherwise between the kidneys of arteriosclerotics and the primary contracted kidney. He says that in spite of some inclination towards the view that the kidneys of arteriosclerotics are different from severe nephritis with arteriosclerosis, he was unable to find any evidence to substantiate it. Histologically the lesions were identical. In the next place, he found it impossible entirely to accept the idea that the genuine or primary contracted kidney is the result of a pure atrophy, because evidence of a certain degree of inflammation was well marked. He reminds the reader that even Ziegler who believed that the process was a pure degeneration, noted evidences of inflammation. Finally Ophuls could not accept the view that the arteriosclerotic interference with the blood supply to the glomerulus was the sole primary lesion in the genuine contracted kidneys, since in some cases the number of affected glomeruli was much too small to account for the extensive lesions found in the tubules and connective tissue.

It must be fairly evident to the reader, from the review of the literature just given that the investigators who have tried to demonstrate that arteriosclerosis is the essential etiological factor in the causation of the primary contracted kidney, have not produced evidence which is convincing. They have all used the histological method; and it is apparently incapable of supplying data of the sort needed to reach a decision in this matter. There is much truth in the idea that the histological picture presented by a tissue exposed to a poison depends on several factors—the dose, the length of exposure and the potency of the poison. If the chemical composition of the substance is such as to place it in the class of powerful poisons and the dose is large, a complete necrosis of the tissue may be quickly

produced. On the other hand, the tissue may be exposed to a sufficiently dilute solution of the same poison for a very long time without showing histological effects. Between these two extremes there lies a broad zone in which the tissue may be found to be acutely or chronically inflamed or degenerated or partly replaced by fibrosis. Widely different histological pictures may thus be obtained from the same poisonous agent by varying the dose and the length of exposure. Can we then reasonably expect to discover the causes of the contracted kidney by the study of anatomical material when we know full well that the factors of dosage and duration—neither of which can be determined—have had at least as much to do with producing the picture before us as the specific character of the unknown substance for which we are searching? Is there not more to be hoped for from the study of the effect upon the kidneys of animals, of substances which are suspected of bearing a causal relationship to chronic nephritis in man? The properly controlled experimental production of a contracted kidney by the use of such a substance would strongly tend to confirm our suspicion that this substance was actually concerned in the causation of human chronic nephritis.

Lead is one such substance and several investigators have succeeded in producing renal sclerosis in animals that have been fed lead salts for a long time. But chronic lead poisoning will account for only a small per cent of the primary contracted kidneys, since only a very few chronic nephritics have been exposed to the ill effects of lead. This exposure is constantly decreasing whereas the incidence of chronic nephritis shows a steady increase.

In order adequately to account for the great prevalence of chronic nephritis, it must be shown that one or more substances or practices in common use, when indulged in to excess, are capable of causing renal and arterial sclerosis. The experience of many able clinicians has emphasized the importance of searching for the etiology of chronic nephritis in some such background as this. Osler, for example, was impressed with the great frequency of chronic Bright's disease in persons who habitually overate. In the 1908 edition of his "Practice of Medicine" he wrote, "It is quite possible that in persons who habitually eat and drink too much, the work thrown upon this organ [the kidney] is excessive, and the elaboration of certain materials

is so defective that in their excretion from the general circulation they irritate the kidneys." While such statements are of very great value as suggestions for further investigation, they, in the absence of both statistical and experimental data, do not add much to our actual knowledge of the causes of Bright's disease.

If overeating injures the kidney, the harmful effects are presumably caused by the abuse of protein, since the fats and carbohydrates are broken down into carbon dioxide which is eliminated by the lungs; and water, which is necessary for renal activity; whereas all the protein is excreted in the form of simpler nitrogenous bodies by the kidneys. It has been shown by Chittenden and more recently by Hinhede (22) that two-thirds of a gram of protein per kilogram of body weight will maintain nitrogenous equilibrium in adults provided their total caloric intake is adequate. This amounts to roughly 55 grams of protein daily for men of average weight. But great masses of humanity habitually eat more than twice this amount; and many individuals eat 150 grams or more daily.

The writer has for some time been studying the injurious effects of high protein diets upon the kidneys (23) and arteries (24) of rabbits. The results thus far obtained as regards the kidneys are briefly as follows. Renal injury was very quickly noted in rabbits that ate several egg whites daily. The addition of egg albumin to otherwise normal food, produced, in the course of some months, well marked deleterious effects upon the kidney. Diets containing casein sufficient to treble the normal nitrogen metabolism caused undoubted renal disease. Rabbits that lived on soy beans (protein about 38 per cent) for months, regularly acquired chronic renal lesions. These animals had a nitrogen metabolism about twice normal. Rabbits that have been fed diets containing beef protein in addition to normal food, so adjusted as to make the protein content about 30 per cent, have repeatedly developed severe renal insufficiency. Many of them have shown blood non-protein nitrogen levels which were two or three times the normal. Some of the rabbits that had been eating the meat mixture for many months presented a clinical picture which suggested uremia. They lost their desire for food to the extent of even being unwilling to eat a carrot. Their bowel movements became loose and black. Within a day or two they were no longer

able to sit up. At about this time muscular twitchings were noted but no generalized convulsions were seen. Death was preceded by coma. The urine of these animals contained much albumin and many casts. The kidneys were always greatly enlarged and under the microscope showed extensive degeneration and atrophy of the tubular epithelium and lesser grades of glomerular involvement.

The results obtained by the use of the soy beans are of special interest since the lesion was produced in an herbivorous animal by a vegetable protein. It sets aside the objection applicable to the egg albumin, casein and beef diets, namely that they are so far removed from anything the rabbit normally eats, that renal lesions obtained by means of these latter proteins are not comparable to the renal disease of man suspected of being due to the abuse of protein. The soy bean nephritis also sets aside another objection to the view that these experiments bear an important relation to human chronic nephritis. It is stated by a critic that the high protein diets must cause a very great disturbance in the acid-base equilibrium with the secretion of a highly acid urine: and that, since the rabbit normally has an alkaline urine, such a shift might in itself be capable of causing the renal injury. As a matter of fact, the urines of rabbits living on the soy beans were invariably alkaline, so that the normal urinary reaction was maintained in rabbits that developed chronic renal disease from eating a high protein diet.

The arteries of rabbits that ate these high protein diets, showed changes of great interest. Every rabbit that ate the casein diet for more three months, every rabbit that ate a meat mixture containing 36 per cent protein for three months or more, and 87 per cent of the rabbits that ate a meat mixture containing 27 per cent protein for six months or more, presented at autopsy the classic picture of arteriosclerosis of the aorta. Furthermore, the extent of the disease was roughly proportional to the duration of the high protein feeding.

Space need not be taken here to discuss the many controls that formed a part of this work. The original publications contain a full account of the sources of error.

It has then been possible to establish a causal relationship between the occurrence of renal and arterial disease in rabbits, and the prolonged ingestion of excessive amounts of protein. The mechanism

underlying this slowly advancing process is at present under investigation. The idea that chronic nephritis might be caused by the absorption from the intestine and subsequent elimination by the kidney of abnormal decomposition products of protein is found repeatedly in the literature, and Harvey (25) has shown that chronic nephritis can be produced by feeding one such substance. Parahydroxyphenylethylamine, isolated by Barger (26) from decomposing meat, and said by Harvey to have been found in the alimentary canal of man, was successfully used by him to produce chronic vascular and renal lesions in rabbits. The writer is at present unable to state whether the lesions obtained by him were or were not related to the absorption of poisonous products arising from the decomposition of the abnormally large amount of protein in the alimentary tract of the rabbits. The presence of foreign protein in the circulation has been shown by Longcope (27) to bear a relationship to chronic renal lesions. He noted that the injection of foreign protein in sensitized animals under conditions which caused anaphylactic shock, was accompanied by the occurrence of focal lesions in the kidneys and some other organs. Such areas were gradually replaced by fibrous tissue, and if the lesions were sufficiently numerous, a fairly generalized sclerosis might result. There appears to be no connection between the chronic nephritis arising from the ingestion of high protein diets and the renal lesions of anaphylactic shock; for first, the renal lesions obtained by the writer were essentially diffuse whereas the nephropathies described by Longcope were distinctly focal; and second, it has been impossible to demonstrate the presence of foreign protein in either the blood or the urine of rabbits that were eating excessive amounts of protein.

What value, in the search for the cause of chronic nephritis in man, should be given to the fact that chronic renal and vascular lesions may be produced in the rabbit by feeding high protein diets? It will be argued by many that effects obtained by means of high protein diets in the herbivorous rabbit can not be properly used to explain similar lesions found in omnivorous man who has become adjusted to the large amounts of protein which he eats. While such an argument can be finally answered only by studying the effect of high protein diets on the kidneys of an omnivorous type of animal, nevertheless

it is of interest to compare the amount of protein eaten by the rabbit when fed a stock laboratory diet with that of man. Investigation of this matter showed that rabbits which were fed oats and carrots ate, on the average, 10 grams of protein daily or at the rate of 5 grams per kilogram of body weight. If a man of average weight ate a corresponding amount, he would consume 350 grams of protein daily. But this comparison is not fair since the proportion of protein absorbed by the rabbit from the food eaten is low, whereas that absorbed by man is high. The amount actually absorbed from the rabbit's intestine on the diet mentioned was at the rate of 2.5 grams per kilo. A corresponding amount for a man of average weight would be 125 grams. Hence it is evident that even though the rabbit normally eats food whose percentage of protein is always low, nevertheless the total mass of food eaten is so much greater kilo for kilo than it is for man that amounts of protein quite comparable with those eaten by man, are in fact also eaten by the rabbit.

Perhaps the comparison between the rabbit and man should be based upon the amount of energy consumed rather than upon the weight, since the rabbit uses about one-third again as much energy per kilo as man. Compared in this way by means of resting metabolism it is found that the rabbit metabolizes about 40 mgm. of protein per calory, whereas a man who weighs 70 kilos and who eats 130 grams of protein, breaks down about 48 mgm. of protein per calory. Here again it is seen that the rabbit uses amounts of protein quite analogous to those of man.

Quite apart from the differences in the food habits of man and of the rabbit, the fact stands out that both arteriosclerosis and chronic renal disease have been produced by a faulty diet. The injury of the small renal arteries was trifling and could not account for the nephritis. This gives an experimental basis for the conception that both diseases are caused by the same poison and makes it no longer necessary to postulate that either is the outcome of the other. Those who believe that that disease of the kidneys which they choose to call vascular nephritis, is caused by atherosclerosis of the glomerular arteries, have thus far offered no convincing evidence to support their hypothesis. Even the most careful examination of such kidneys will not establish the time relations existing between the disease of the renal arterioles and of the remainder of the kidney.

Recently Squier and Newburgh (28) have performed experiments which show that the abuse of protein by man will very quickly give evidence of renal injury. Five medical students whose urine was qualitatively and quantitatively normal each ate at noon and again at 6 o'clock a beef steak averaging about $1\frac{1}{2}$ pounds in weight. In every case, red blood cells were found in the urine passed in the late afternoon as well as in the urines collected during the night. Three of the urines voided the next day still showed a few red blood cells. A group of patients suffering from so-called essential hypertension in whom urinary evidence of kidney disturbance was slight or absent, were subjected to a high protein regime for one or more days. This resulted in the appearance of albuminuria in the patients who had not previously shown it, an increase in the fundus changes and the presence of red blood cells in the urine of every case. Still more striking effects were obtained in cases of frank nephritis.

These experiments show that man has not yet developed kidneys which can, without suffering injury, excrete the products of a protein ingestion little if any higher than that indulged in by great masses of humanity and they give support to the hypothesis that the long continued abuse of protein makes of the renal apparatus a "locus minoris resistentiae." Such a weakness would greatly increase the likelihood of further damage by infection. An occurrence during the world war seems to bear out this supposition. Shortly after the appearance of acute upper respiratory infections there was a wave of hemorrhagic nephritis in the British Expeditionary force. The subsequent statistical study of the records showed that there had been no acute nephritis in the contingent from India. This seemed the more surprising since the Indian troops had been much more seriously affected by the respiratory infection than had the European British soldiers. When the rations of the two groups is compared it is found that the British, according to Abercrombie (29) were daily consuming 180 grams of protein whereas the Indians who only consented to come to Europe when assured that they could continue their native diet, ate daily about 90 grams of protein. May not the large amount of protein in the British ration, an amount three times the requirement, have jeopardized the kidneys of the British soldiers to such an extent as to make them an easy prey for an infection which

when it encountered the normal Indian kidneys was unable to harm them?

It is well known that chronic nephritis is relatively rare amongst tropical peoples and that it is one of the commonest diseases seen in the temperate zone. Dr. P. W. Harrison bears witness to the scarcity of nephritis in one tropical race in the following passages contained in a recent letter from him:

> Taking for consideration the inland shepherd Arabs, commonly called Bedouins, we have a well defined group whose protein consumption as well as their calory intake is exceedingly low. Their usual diet is composed of a few dates and some camel milk and little else. It is only on rare occasions that they taste meat. Among the members of this group, nephritis is so rare as to be practically unknown. In ten years practice among them, I can recall but one case of this disease, and that an acute juvenile case, probably due to frank infection. Many of our hernia cases come from this group and the routine examination of their urines has only served to confirm this opinion of the rarity of any kidney disturbance among them.

In the United States, on the other hand, there were in 1915, 909,155 deaths of which 70,500 were due to nephritis.

It is also well known that Europeans and North Americans consume much larger amounts of protein in the form of animal food than do the native tropical races. May not the excessive protein metabolism of Northern peoples be partly or even largely responsible for the high incidence of chronic nephritis amongst them?

In conclusion, the writer ventures to set down the idea that chronic nephritis is, generally speaking, caused by the combined effect of infection and abuse of protein.

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SUBACUTE BACTERIAL ENDOCARDITIS

GEORGE BLUMER

It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future.—*William Osler, Gulstonian Lectures, 1885.*

HISTORICAL

The first unmistakable record of the clinical picture of the prolonged form of infectious endocarditis which the writer has been able to find is in an article "On some of the principal effects resulting from the detachment of fibrinous deposits from the interior of the heart and their mixture with the circulating blood." This article, which contains a clear description of the remote mechanical effects of endocarditis, is by W. Senhouse Kirkes and was published in 1852. In 1868 Samuel Wilks, in an article on "Pyaemia as a result of endocarditis," described a case of infectious endocarditis of six months duration, substantiated the diagnosis by autopsy, and called attention to the fact that at that time endocarditis had never been systematically considered in the text books on medicine. In 1869 Quinquad described a prolonged case of infective endocarditis, and in discussing this disease said: "Mais il existe en outre une forme chronique de l'endocardite ulcereuse dans laquelle les infarctes viscéreaux peurent se produire et les accidents généreaux faire défaut." In 1873 Lancereaux, in an article on the relation of paludism to ulcero-vegetative endocarditis, gave a clear and concise description of the outstanding signs and symptoms of subacute bacterial endocarditis. He described the condition as a definite type of endocarditis occurring in patients who had suffered from malaria, doubtless because most of his patients happening to be soldiers who had been in the tropics or returned colonials, acquired that disease. It is clear that about this time Rapin, who

did not publish his observations until thirty years later, also recognized the disease and gave a fairly accurate description of the peculiar skin lesions now commonly known as Osler's sign. These were even more accurately described by Heubner in 1899 and were clearly recognized by Münzer in 1900. In 1880 Byrom Bramwell briefly noted the occurence of prolonged infectious endocarditis in his text book and mentioned a case of Murchison's. In the following two years Bristowe and Coupland described typical cases. In 1882 Leyden called attention to the disease, more particularly to the "pseudomalarial" type later emphasized by Osler (1893), Dock (1895) and Coleman (1905). In 1885 Osler, in his Gulstonian Lectures, first adequately called attention to the disease in its varied forms, and two years later Stern and Hirschler of Koranyi's Clinic emphasized its protean symptomalogy and its deceptive remissions and intermissions. In 1891 Fraentzel mentioned the condition in his book on the heart. In 1896 Samuel West described the first case of the type simulating splenic anaemia later noted by Parkes Weber (1910), Osler (1912), Riesman (1918), and Auerbach (1920). In 1899 Mabel Austin described the first cases due to Bacillus influenzae, Heubner emphasized the relation to obscure continued fever, Ebstein stressed the frequency of the condition, and Harbitz published the first satisfactory description of the pathological anatomy and histology. During 1899 and 1900, Litten, and in 1901 Lenhartz published valuable papers, and since the beginning of the present century an increasing appreciation of the importance of the subject shows in the increasing number of contributions. Reference cannot be made to all of these but the more important are those of Koeniger, Löhlein, Libman, Coombs, Gaskell and Baehr on the pathological side; those of Schottmüller, Rosenow, Horder, Major, Kinsella and Fox and Lynch on the bacteriological or serological aspects; and those of Osler, Libman, Frank Billings, Jochmann, Marchiafava, Lutembacher, Vaquez and Kastner on the clinical manifestations. Excellent reviews have been furnished by Horder, Simons, Libman, Vaquez and Debré. The work of the present century has emphasized the varied clinical types of the disease, the almost constant relationship to infection with a certain type of streptococcus and the characteristic pathological lesions.

TERMINOLOGY

A survey of the literature of endocarditis and a study of case reports makes it clear that the *course* which an attack of bacterial endocarditis may run varies within very wide limits. The disease may be fatal within a few days of onset or the patient may survive considerably over a year, even two and a half years in exceptional cases. It is also apparent that no sharp line can be drawn between the acute, the subacute and the chronic forms. It seems nevertheless true that in most instances the disease either terminates in a relatively short time, i.e., three to seven or eight weeks, or else lasts for a period better measured by months. Some writers have suggested that cases lasting two months or over be classed as subacute, and others have proposed three months as the minimum period. As a matter of fact the cases lasting under three months form a very small minority and for that reason the case reports which have been analyzed to form the basis of this review have been chosen on a three month minimum time basis with a full appreciation of the fallacies which are inherent in this method. It seemed better to the writer, as it did to Libman and Horder, to classify all the protracted cases as "subacute" rather than to complicate matters by attempting to make still another artificial time division separating the subacute from the chronic.

For purposes of clarity it is necessary to point out here that a variety of different names has been given to the condition we are discussing, and that the one we have chosen, Subacute Bacterial Endocarditis (Libman) has been selected because it seems less open to misinterpretation than any other. Some writers have contented themselves by describing this particular type of endocarditis as chronic, or protracted, but the majority have suggested a definite terminology. The condition has been called "chronic septic endocarditis" (Heubner) "malignant rheumatic endocarditis" (Litten), "rheumatoid form of septic endocarditis" (Litten), "Monadine" (Klebs), "forme febrile prolongee de l'Endocardite maligne" (French School), "chronic streptococcus endocarditis" (Horder), "chronic malignant endocarditis" (Weber), "endocarditis lenta" (Schottmüller), "subacute infective endocarditis (Libman and Celler), "subacute bacterial endocarditis" (Libman), "chronic ulcerative endocarditis," "chronic septicaemic endocarditis" (Riesman), "endocarditis septica lenta"

(Lossen), "endocardite maligne à marche lente" (Roger), "subacute streptococcus and influenzal endocarditis" (Libman), "Endocardite maligna a decorso lento" (Italian School), and "endocardite a forma infettiva prolongata (Vaquez).

The objections to some of the qualifying adjectives which have been used to describe this type of endocarditis have been frequently discussed, particularly by Simons in his critical review. The term "malignant," he says, is bad because all cases are not fatal, an objection which has little force in view of the great infrequency of recovery. If any form of endocarditis is entitled to the description malignant it is surely this type. However a more forcible objection, we think, is that the term throws no light upon either the etiology or pathology of the disease. The term "septic" is objected to by Simons because there is no pus formation. There are many septic processes in which pus formation is lacking and the term does not necessarily call to mind the picture of suppuration. The same objection holds here that held in regard to the use of the term malignant. The term "ulcerative" is open to the objection that the lesions are much more frequently proliferative than destructive. The term "infectious" is too vague as it would include rheumatic and syphilitic endocardial lesions. Bacterial endocarditis seems least open to objection especially if, in a given case, the name of the specific causative bacterium be substituted for the word bacterial. We would then speak of subacute streptococcus endocarditis or subacute pneumococcus endocarditis. Strictly speaking there are objections also to the term bacterial because tuberculous endocarditis is also a prolonged bacterial type, but this form is so extremely rare that for all practical purposes it may be disregarded.

PREVALENCE AND IMPORTANCE

There are unfortunately few accurate figures covering the frequency of subacute bacterial endocarditis as compared with the three other common infectious types, the rheumatic, the syphilitic and the acute bacterial. Lenhartz says that 42 per cent of cases of infectious endocarditis are of this type, Horder says only 12 per cent. The earlier writers, Osler for example, while realizing the importance of the condition were perhaps not sufficiently impressed by its frequency. It

is not until almost the beginning of the present century that we find statements concerning this. Ebstein in 1899 says: "Chronic cases of ulcerative malignant endocarditis are much more frequent than has formerly been supposed." E. G. Janeway in the same year suggests that the disease is increasing in frequency. Lenhartz in 1901 says that "it is far too little known up to the present that true septic Endocarditis can run such a protracted course," and Jochmann ten years later makes the same observation. Debré in 1917 says that "the condition is insufficiently known," and again in 1919 remarks that "it is not very rare." Libman in 1918 says that "the frequency of the disease has been much underestimated." Thomas. Lewis in 1920 says that "the disease is not uncommon but is often overlooked." Morawitz in 1921 states that "it is not known to the profession generally." It is clear that in some places the disease is far from rare; Libman in 1918 stated that he had seen nearly three hundred cases personally. Frank Billings incidentally remarked that he had seen over one hundred cases. Schottmüller states that exclusive of rheumatic Endocarditis it is the most frequent form of the disease. Horder says that in a general medical service the disease appears about once in every two hundred ward patients, and Cotton states that 8 per cent of invalided soldiers with gross valvular disease had subacute bacterial endocarditis. Libman states that 0.3 per cent of patients with chronic valvular disease die of subacute bacterial endocarditis. On the other hand there is some evidence which suggests that the disease is not equally prevalent in all parts of the civilized world. Steinert (1910) says that the subacute form is not the most frequent form in Leipzig. Gouget (1913) states that "it is an exaggeration to say with Schottmüller that it is the most frequent form of infectious endocarditis."[1] These obvious differences of opinion are doubtless due partly, at least, to lack of agreement as to the class of cases to be included under the term infectious endocarditis and partly perhaps, as suggested above, to differences in regional distribution. In New Haven the subacute bacterial type of endocarditis appears much more frequently in the medical wards and in private practice than the acute type, if we exclude the rheumatic cases and

[1] Schottmüller did not say this. He specifically excepted the rheumatic type.

those which are terminal and often clinically latent. It is difficult to say whether the disease is actually increasing or whether there is merely an apparent increase due to increasing ability on the part of the profession to recognize the condition. Personal experience would rather favor the latter view, though Morawitz strongly inclines to the view that the disease has increased in Germany since the war.

PATHOLOGY[2]

General Considerations

The lesions of infectious endocarditis, whether acute or subacute, are due to the action of two factors: (1) the toxic factor, a necessary accompaniment of an infectious process, and (2) the mechanical factor, the lodgement of emboli of various sizes detached from the diseased endocardium. In subacute bacterial endocarditis a third factor is frequently added owing to the fact that this disease is often grafted upon an already damaged heart. The changes in the heart and internal viscera which accompany the different valve lesions with their varying degrees of cardiac subcompensation or decompensation are therefore commonly a part of the pathological picture. It hardly seems desirable in an article of this scope to go into minute detail regarding the well known toxic and embolic phenomena common to all forms of endocarditis or the equally well known lesions of cardiac decompensation. We shall rather aim to emphazise the peculiarities which distinguish the lesions of subacute bacterial endocarditis from those of other forms.

Cardiac Lesions

The lesions in the heart present three outstanding peculiarities: (1) implication of valves already damaged by previous endocarditis; (2) involvement of the mural endocardium and chordae tendineae, and (3) relatively slight impairment of the myocardium. Before discussing these characteristics the other less specific findings in the cardiac pathology may be briefly reviewed.

[2] Based on an analysis of 150 autopsies recorded in the literature or personally observed.

It is to be noted that various combinations of cardiac hypertrophy and dilation occur, as would be expected in the presence of both old and fresh valvular lesions. The usual changes associated with mitral disease or aortic disease or combined valve lesions are found. *Very slight hypertrophy* is noted in just under 6 per cent of 84 autopsies in which there is definite information as to the size of the heart, and an equal proportion is stated to show *no enlargement of the heart.*

The *pericardium* does not, as a rule, show marked lesions. Obliteration of the pericardial sac is recorded in 3.3 per cent of the autopsies, and an equal percentage shows varying degress of hydropericardium. Subpericardial ecchymoses are common, and acute or subacute pericarditis is noted in 4.6 per cent of the records.

The character of the *endocardial lesions* has been well described by Harbitz, by Litten, by Libman and by Orth. The lesions of the valves tend in most cases to be proliferative rather than destructive, and take the form of small verrucose excrescences or larger polypoid masses. In some instances enormous thrombotic vegetations are produced, as recorded by Orth and others. Extensive destruction of the valve sails may occur, and the verrucose or polypoid outgrowths may be attached to the valve stumps. The vegetations vary in color as they do in contour; some are described as grayish, others as pinkish, and still others are stated to have a distinctly greenish hue. A decided tendency to healing is an outstanding feature in many of the endocardial lesions (Harbitz, Libman), the vegetations being usually firm in texture and frequently showing calcification at the base. Perforation of a valve was noted 8 times in 150 autopsies and valve aneurysm 7 times.

Inasmuch as subacute bacterial endocarditis is almost exclusively a disease of adult life it is the *valves of the left side* of the heart which are chiefly involved. Among the 150 autopsies were 4 in which the fresh process attacked the mural endocardium (1), or the pulmonary artery only (3), leaving 146 cases in which the fresh process involved the valves.

The following table shows that in the great majority of instances the mitral and aortic valves were the ones implicated:

	cases	
Mitral valve only involved	58	
Aortic valve only involved	16	*
Mitral and aortic valves involved	56	
Pulmonic valve only involved	4	
Tricuspid valve only involved	3	
Mitral and tricuspid valves involved	1	
Aortic and tricuspid valves involved	3	
Aortic and pulmonic valves involved	1	
Mitral, aortic and tricuspid valves involved	4	
	146	

*130 cases or 89 per cent.

It should be noted that the very high figures of combined mitral and aortic involvement are largely due to the recent aortic disease involving the aortic leaflet of the mitral valve. The cases of pulmonary artery involvement are decidedly unusual and are all of them contributed by one observer, Lutembacher.

The *coronary arteries* seldom show pronounced lesions. In the 150 autopsies, thrombosis and embolism are each noted only once and coronary sclerosis 3 times. There were in addition 2 cases with infarction of the myocardium, probably embolic in origin. In view of the relative frequency of cardiac pain as a symptom and the current conception of the role of the coronaries in its production this lack of evidence of coronary disease is rather astonishing. It should, however, be stated that the autopsy records vary very greatly in their completeness, and it may well be that special study of the coronaries would reveal more frequent lesions.

Of the peculiarities of cardiac pathology which need special discussion the first to be noted is the tendency of *subacute bacterial endocarditis to attack damaged valves.* Practically every writer who has discussed the subject has commented on this point. In 150 recorded autopsies there were 58, or slightly over 38 per cent, in which definite evidence of old valve lesions was noted. There were also 2 instances of fibrous pericarditis and 5 of chronic interstitial myocarditis in which no old valve lesion was noted. There was therefore evidence of old cardiac damage in 65 out of 150 autopsies i.e., in 43.3 per cent. It may be stated quite certainly in view of the clinical figures regarding the rheumatic group of infections in these patients, and in view of

the imperfect autopsy records in a good many cases, that this figure is very decidedly an understatement of the true condition. There is no doubt whatever that more careful study of the hearts of patients dying from subacute bacterial endocarditis would show a much larger percentage with old cardiac lesions.

It is necessary to point out that the reinfection may involve other parts of the heart than a previously infected valve. The following analysis of 65 well recorded autopsies illustrates this point:

	times
Reinfection of a previously damaged valve occurred	28
Infection of a presumably normal valve with reinfection of a damaged valve	19
Infection of a normal valve without reinfection of a previously damaged valve	6
Mural infection without reinfection of a damaged valve	4
Original infection mural, pericardial or myocardial; reinfection valvular	8

The above figures are important in the discussion of the pathogenesis of cardiac reinfection, a discussion which, on account of the bearing of certain clinical facts, will be deferred until later.

The second special peculiarity in the cardiac pathology of subacute bacterial endocarditis is *the frequency with which the mural endocardium is involved* as contrasted with other types of endocarditis. In the 150 autopsies analyzed it was found that in 83, or 55.3 per cent, the walls of the cardiac cavities, the chordae tendineae or the intima of the aorta or pulmonary artery were involved either alone or in conjunction with the valvular endocardium. In 6 of these cases rupture of the chordae tendineae was noted. These figures, too, undoubtedly err on the side of conservatism as small lesions of the chordae or the mural endocardium could easily be overlooked. This mural involvement is emphasized not because it is pathognomonic of the subacute form of endocarditis but because it is of such great frequency in this condition that its presence always suggests this type of the disease.

The third special peculiarity in the cardiac pathology of subacute bacterial endocarditis, the *relatively slight involvement of the myocardium*, is perhaps less striking than the preceding ones. In the 150 autopsies collected pathological conditions of the myocardium are mentioned only 30 times and in 12 instances the recorded lesion is an evidence of toxemia, such as generalized fatty degeneration or cloudy swelling. Chronic interstial myocarditis is noted 8 times, acute

myocarditis only twice, small abscesses in the heart muscle 3 times, focal necroses twice and infarct twice. This relative freedom of the myocardium from damaging lesions fits in well with the clinical observation that signs of serious myocardial impairment are singularly lacking in the early stages of the disease and usually appear only as terminal events.

Extracardiac lesions

The lesions of subacute endocarditis found elsewhere than in the heart are either mechanical, infectious, toxic, or embolic. There are three of them deserving of particular discussion: (1) the vascular lesions; (2) the visceral infarcts, and (3) the peculiar kidney changes.

The *mechanical lesions* which are found in subacute bacterial endocarditis are those usually associated with valvular heart disease in various stages of subcompensation or decompensation. In the 150 autopsies chronic passive congestion or hypostatic congestion of the lungs is noted 30 times, hydrothorax 8 times, chronic passive congestion of the liver 53 times, and ascites 4 times. These lesions do not assume the prominence which they hold in autopsies on patients dying from cardiac decompensation because this condition is, as a rule, of minor importance both in the genesis and the course of subacute bacterial endocarditis. It is to be noted that in addition to these chronic phenomena many patients show terminal mechanical changes such as pulmonary edema.

The rôle of *infection* other than the original sepsis, is not a striking one in subacute bacterial endocarditis. Nevertheless it is interesting to note that lesions denoting secondary infection are by no means unknown. Terminal bronchopneumonia is noted 12 times in the 150 autopsies, and this figure would doubtless have been larger if histological examinations had been made in all cases. Lobar pneumonia is noted 3 times, pleurisy 12 times, and perihepatitis once. There are also inflammatory lesions which seem clearly to be expressions of the embolic manifestations of the original sepsis. Abscesses in the myocardium, abscesses in the lung, abscess of the liver, acute pericarditis, acute peritonitis, acute meningitis, tracheobronchial or intraperitoneal lymphadenitis and subcutaneous abscess. The autopsy bacteriology in most of the recorded cases is unfortunately too incomplete to per-

mit us to say definitely whether the original infection or secondary infection caused these focal lesions. Certainly from clinical experience it is reasonable to assume that in some instances death is due to terminal infection with organisms other than those causing the endocarditis; terminal erysipelas or terminal pneumonia for example. This, of course, might be expected from analogy with other protracted infectious diseases, such as leprosy or tuberculosis, the subjects of which not infrequently succumb to infection with more virulent organisms.

The evidences of *toxemia* show themselves in the various viscera in the usual way. Cloudy swelling of the myocardium, the liver and the kidneys is common and is sometimes associated with fatty degeneration. Acute spleen tumor is of frequent occurrence. Degenerative changes in the pancreas and adrenals are occasionally noted. Swelling of the lymph nodes is rather conspicuous by its absence, but we suspect that more exact records would have shown lymphadenitis to be more common. In exceptional cases great enlargement of the mediastinal and peritoneal nodes has been noted and occasionally the superficial nodes also are involved. Doubtless in many instances the effects of infection are combined with those of toxemia.

Of the special features in the general pathology of subacute bacterial endocarditis the gross *vascular lesions* while more spectacular are less important than the visceral embolic features. The most frequent vascular lesion, as might be expected, is *embolism*. The aorta, the pulmonary artery, the coronaries, the iliacs, the arteries of the extremities, and above all the cerebral vessels are noted as the site of emboli. A very similar group of vessels is recorded as the site of arteritis and thrombosis—so similar that, knowing the difficulty of distinguishing arterial thrombi from emboli, one suspects that most of the cases of arterial obstruction are of embolic origin. In all, 21 instances of arterial obstruction are noted in the 150 protocols as follows:

	times
Pulmonary artery	4
Middle cerebral artery	3
Aorta and brachial artery, each	2
Radial, coronary, iliac, nasal, each	1
Anterior tibial, basilar, mesenteric, each	1
Internal carotid, splenic and hepatic arteries, each	1

The occurrence of *thrombo-phlebitis* is noted in 6.6 per cent of the autopsies and inasmuch as this lesion is easily overlooked in small vessels it is reasonable to suppose that it is more often present than the figures indicate. The veins of the lower extremities were involved in 6 of the 10 recorded cases, the iliacs and femorals each twice, the popliteal and internal saphenous each once. The other veins involved were the subclavian, pulmonary, portal and veins of the bladder.

Embolic aneurysms are noted 9 times in the 150 autopsies, 3 times in the cerebral arteries, twice in the aorta, and once each in the femoral, iliac, superior mesenteric, and ulnar arteries. There is direct bacteriological evidence in a few instances of local infection of the vessel wall. Libman thinks some aneurysms are due to the mechanical action of calcific splinters. In most instances the aneurysm was of pathological rather than clinical significance, though in the few cases where superficial vessels were involved the lesion was diagnosed clinically. Simmonds has called attention to the importance of small aneurysms of the cerebral vessels in the causation of cerebral hemorrhage, pointing out that a small proportion of the fatal cerebral complications are not due to embolic softening but to rupture of a small aneurysm.

The striking feature of the *embolic manifestations* of subacute endocarditis as contrasted with those occurring in the acute form of the disease is the *lack of suppuration*. However, it is to be noted that in the 150 autopsies septic infarcts or focal abscesses were noted 23 times. Among 24 instances of pulmonary infarction there were 3 infarcts that suppurated, in 115 infarcted spleens suppurating infarcts were noted in 16, in 64 infarcted kidneys suppuration was noted twice and among 35 brains showing evidence of embolism 2 showed abscesses. As mentioned previously there were 3 instances of abscess in the heart muscle, and 1 or 2 instances of localized subcutaneous suppuration. Failure of the emboli in various organs to produce suppuration is therefore relative rather than absolute, indeed in certain instances where multiple infarcts were present in an organ some suppurated and others did not. Doubtless the explanation of this lack of suppuration lies chiefly in the low virulence of the infecting organisms, but it may be due in part to the very small number of organisms present in some

emboli and in part to individual peculiarities of tissue resistance. Letulle's suggestion that we should speak of pyogenic individuals rather than pyogenic organisms, while perhaps an exaggeration, contains at least some elements of truth.

The *kidney lesions* which occur in subacute bacterial endocarditis present, in the majority of cases, definite peculiarities. These are usually found in infections with the streptococcus viridans but Horder has described one instance in an infection with B. influenzae, and Gaskell one in a pneumococcus infection. These characteristic lesions were first pointed out by Löhlein in 1910 and their occurrence has since been confirmed by the studies of Baehr, of Gaskell, and of Baehr and Lande. The macroscopic appearance of the kidneys is quite characteristic in many instances. The organs are only moderately enlarged, weighing from 150 to 240 grams. They are usually smooth, and the surface is covered with punctate hemorrhages to such an extent that Gaskell has called them "fleabitten" kidneys. Histologically the lesion is described by Löhlein as an embolic focal nephritis (embolische Herdnephritis). As suggested by Löhlein and demonstrated by Baehr and by Gaskell the lesion is due to the lodgment in the glomerular capillaries of bacterial emboli. Baehr states:

"The salient features of the lesion which serve to differentiate it from other types of glomerular disease are: first, the involvement of one or more loops of a variable number of glomeruli; second, the absence of any visible disease in the uninvolved glomeruli and in the uninvolved portions of affected glomeruli, and third, the association in most of the bacterial cases of all stages of the glomerular process, often seen in a single microscopic section."

The histological picture varies in different stages of the process. The earliest lesion is a swelling of the glomerular epithelium in the affected portion of the tuft followed by fusion of the involved cells into a homogenous granular mass containing degenerating nuclei, which subsequently become completely organized and clothed by a reflection of the epithelium of the adjacent Bowman's capsule. During the acute stages of the process there may be a fibrinous exudate in the capsular space containing red blood corpuscles and polynuclear leucocytes, the latter cells also occurring to some extent around the

capsule. Groups of lesions in varying stages of development are found in the kidneys from patients who have died during the bacterial stage of the disease, while only healed lesions are found in those dying in the bacteria free period. On account of the patchy distribution of the lesions and the freedom of considerable areas of glomerular tissue from involvement *serious impairment of kidney function does not occur in uncomplicated cases.* The studies of Baehr and Lande have shown, however, that in a certain proportion of patients either an acute diffuse glomerulonephritis or a chronic diffuse nephritis of the type of the secondary contracted kidney occurs, with very serious impairment of kidney function and not infrequently death from uraemia.

In 3 cases, 1 recorded by Ebstein, 1 by Koeniger and 1 personally observed case, *nephrolithiasis* was present. In Koeniger's case there is nothing in the record to indicate any special peculiarity in the stone formation. In Ebstein's case it is noted that small stones (Steinchen) were present in the pelves of the kidneys and the bladder. The personally observed case was remarkable for the great number and small size of the stones. Dr. Winternitz' note concerning them reads as follows:

"Perhaps the most striking feature is the innumerable fine calculi which are found in the pelves of both organs. These almost fill the pelves, which however, are not dilated. The smallest of these calculi is no larger than a grain of sand; the largest several millimeters in diameter. The ureters are delicate, but contain occasional calculi similar to those described in the pelves of the kidneys."

Cultures from the calculi remained sterile. There seems no doubt that the formation of these calculi was contemporaneous with the infection but their exact relationship to the process is not clear.

Bearing of pathology on clinical manifestations

The bearing of certain of the pathological lesions of subacute bacterial endocarditis upon the clinical picture of the disease can best be emphasized at this point. So far as the heart is concerned it is to be noted that the localization of the inflammatory process on already damaged valves and its situation and character result in conditions which frequently *do not cause any change in the preëxisting physical*

signs. This statement must not be taken too literally but in a general way it is correct. The localization of the endocardial lesions on the chordae tendineae and mural endocardium does in some instances reveal itself by the *appearance of new murmurs* which, in the case of rupture of a chorda, may develop very suddenly. The relatively slight involvement of the myocardium is responsible for the lack of obvious enlargement of the heart which occurs in about twelve per cent of the cases, and is also responsible for the absence of the signs of decompensation in a majority of the patients. Of the peculiarities of the extracardiac lesions which bear on the clinical picture the most important is the lack of suppuration in the embolic lesions. This peculiarity is certainly responsible in part for the comparatively low type of fever which accompanies the disease and the frequence with which patients recover from embolic lesions which, if due to septic emboli, would much more frequently prove fatal.

ETIOLOGY[3]

Predisposing causes

Before considering the exciting causes of subacute bacterial endocarditis certain predisposing factors, namely, age, sex and previous disease, must be discussed.

The following table is based upon 317 case records in which the *age* of the patient is mentioned:

YEARS	CASES
1–10	1
11–20	54
21–30	116
31–40	86
41–50	37
51–60	19
61–70	4

I can find no comparable table but there are scattered references in the literature covering smaller groups of cases. Of Rosenow's 14 cases[4] 11, or 78 per cent, were between 15 and 29 years of age.

[3] Based on the records of 294 cases from the literature and 36 personally observed.

[4] Included in my table.

Horder says that 50 per cent of the cases occur between 20 and 40 (my figures show 56 per cent). Debré says that 66 per cent of the cases occur between the ages of fifteen and thirty. Of Libman's 150 patients 142 or 94 per cent were between 10 and 50 years of age. Analysis of the table presented above shows that 80.75 per cent of the cases occurred between the ages of 11 and 40. Between 11 and 50, 86 per cent occurred, giving figures comparable with those of Libman. These figures indicate that subacute bacterial endocarditis is a disease of adolescents and young adults. In other words *the disease occurs during the period of greatest incidence of valvular heart disease,* excluding the types due to syphilis and arteriosclerosis.

With regard to *sex* the records of 328 cases in which the sex is mentioned show 197 males, or 60 per cent, and 131 females or 40 per cent. These figures are in accord with Osler's view that valvular disease is more frequent among men than among women, a view which, however, is disputed by some good observers, notably Jurgensen. The number of cases analyzed is, however, hardly sufficient to be more than suggestive.

The *relation of previous disease* to subacute bacterial endocarditis is of interest from two viewpoints: (1) the question of the portal of entry of the infecting agent, and (2) the predisposing effect of antecedent infections, particularly the rheumatic group, and of cardiac damage antedating the bacterial endocarditis.

The question of the *portals* by which the bacteria which cause subacute bacterial endocarditis enter the circulation is difficult to decide in the majority of instances. According to Venning it is possible to find a probable portal of entry in infectious endocarditis in only about 27 per cent of autopsies. This figure, which covers acute as well as subacute cases, gives some indication of the difficulties of finding such a focus clinically. Among 330 cases analyzed a probable, or at least possible, portal of entry is recorded 58 times, i.e., in 17 per cent of the cases. The following table gives the figures:

	times
Teeth	17
Tonsils	16
Female generative organs	13
Bronchi	5
Wounds or injuries	4
Gall bladder, male genitalia, furunculosis, each	1

This list corresponds fairly closely with the portals of entry which are usually suggested by writers on the subject. However, other probable sources of infection are noted from time to time. Pneumonia, grippe, otitis media and disease of the accessory nasal sinuses (Billings), catheterization (Lenhartz), appendicitis and cholecystitis (Babcock), and venesection or improperly administered intravenous injections (Lutembacher) have all been suggested. Schottmüller and the English school of clinicians place a good deal of emphasis on infection through the intestinal tract.

The finding of the primary focus in many patients is a practical impossibility. Insidiousness is one of the striking characteristics of the disease, and in many instances a local infection which might be the source of the general sepsis could have cleared up, leaving no trace, before the search for a focus was begun. Then too, it is a practical impossibility to locate small latent foci in the sinuses, the bones and the internal organs, and it must not be forgotten that there is a good deal of evidence that bacteria may gain entrance to the circulation through insignificant local lesions and possibly without producing any appreciable local damage. The studies of Davis, which show that the pneumococcus occurred in the tonsils removed from 4 out of 10 patients with endocarditis, are of interest in this connection, as are also the observations of Schottmüller who found streptococcus viridans in conjunctivitis, rhinitis, bronchitis, thrombophlebitis, lung abscess, empyema, pericarditis, pylephlebitis, appendicitis, peritonitis, pancreatic necrosis, and enteritis. Furthermore in several instances under the author's observation, and some recorded in the literature, it has been possible to isolate Streptococcus viridans from root abscesses at a period when it was also present in the blood. Stadler has seen infection follow tooth extraction. The observations of Henrici and Hartzell showing the great frequency with which streptococcus viridans is found in pulpitis and peridental lesions are of fundamental importance.

The relationship of previous infections, and particularly of *antecedent rheumatic infection*, to subacute bacterial endocarditis is of such frequent occurrence that it has arrested the attention of all students of the disease. The following table indicates the frequency with which different infections have been incriminated by various authors

as predisposing factors in the etiology of subacute bacterial endocarditis. In this table only the disease thought to be of major importance in a given case has been included. Needless to say various combinations of rheumatism with chorea and tonsilitis, and also other infectious processes occurred in some patients, but it seemed less confusing to note only the major infection. Usually an infection has been assumed to be of major importance because definite evidence of cardiac damage followed it.

In 330 cases there was a history of:

	times	
Antecedent rheumatism	140	*
Antecedent tonsilitis	18	*
Antecedent chorea	10	*
Antecedent pneumonia	5	
Antecedent scarlet fever	3	
Antecedent dysentery, influenza, gonorrhea and syphilis, each	1	

*168 or a fraction over 50 per cent.

A definite history of an infection of the rheumatic type, including in this group rheumatism, chorea and tonsilitis, was therefore present in 50 per cent of the patients, which is exactly the estimate given by Horder in 1920. Other observers evidently think that a preceding rheumatic infection is much more frequent than this. Thus Libman and Celler (1910) state that there is nearly always a history of rheumatism, and Debré (1919) states that a past history of rheumatism is almost constant. It is quite probable that if all of the recorded histories had been taken with the possibility of rheumatism in mind the percentage of patients with rheumatic history would have been larger. Venning's carefully analyzed records covering all types of infectious endocarditis showed a history of rheumatism in nearly 60 per cent.

The history of *an old valve lesion* preceding the subacute endocardial infection is so intimately connected with the history of rheumatism that the two must be considered together. In the 330 records analyzed there was a history of:

	times
Rheumatism with old valvular lesion	81
Tonsilitis with old valvular lesion	5
Chorea with old valvular lesion	3
Pneumonia with old valvular lesion	5

Scarlet fever with old valvular lesion	3
Gonorrhea, syphilis, influenza and dysentery with old valve lesion, each	1
Old valvular lesions of unknown origin	22
Congenital heart disease	2
	122

In addition there were 2 cases with the cardiac changes of hyperthyroidism, 2 cases of cardiac hypertrophy without valve lesion, 1 case of healed pericarditis, 1 case of athletes' heart and 2 cases of luetic aortitis. In all, there were 113 cases, or 34.2 per cent, in which a definite history of cardiac damage preceding the subacute endocarditis could be obtained. On the other hand there were only 47 cases in which it is definitely recorded that no old cardiac lesion was present, leaving 170 patients, many of whom had rheumatism or other infections, concerning the condition of whose hearts before the final endocarditis there is no definite knowledge. We may safely assume that in considerably more than one third of the patients who contract subacute bacterial endocarditis the process is grafted on an old cardiac lesion.

The figures just presented at once raise the question of the *relation of the rheumatic group of infections and of old valve lesions to subacute bacterial endocarditis*. Does rheumatism predispose to subacute bacterial endocarditis because it damages the heart, or is it a predisposing factor irrespective of cardiac injury? A satisfactory answer to this question is blocked at the very outset by the fact that we do not know the etiology of rheumatism. We can discuss the question but only by assuming certain points of view which so far have not been generally accepted.

It is hardly within the scope of this article to enter on a minute discussion of the etiology of rheumatism, yet this must be touched upon in order to clear the ground. Certain observers regard rheumatism as a form of streptococcus sepsis. Singer, for example, says, "It is to be classified as a variety in the great disease family of the pyaemias." Others, equally competent, believe that the rheumatic virus has not been discovered, but admit that this disease, like scarlet fever and small pox, predisposes the patient to secondary bacterial invasion, particularly with organisms of the streptococcus group.

Assuming, for the purpose of argument, that rheumatism is of unknown etiology the next question which arises is whether the usually non fatal verrucose endocarditis which so commonly complicates this disease is due to the rheumatic virus or to secondary invaders. Several competent observers have examined heart valves which were the site of rheumatic endocarditis both histologically and bacteriologically with entirely negative results. On the other hand at least one recent observer, Reye, found streptococcus viridans culturally in 8 out of 23 cases of verrucose endocarditis, several of which were of rheumatic origin. Histologically rheumatic hearts show certain peculiar and apparently specific lesions, the so-called Aschoff nodes. The studies of Coombs have shown that these are *not* present in hearts from patients dead of subacute bacterial endocarditis. We find the same differences of opinion regarding rheumatic endocarditis as exist regarding rheumatism with two chief views, one regarding the endocarditis due to the rheumatic virus the other regarding it as caused by streptococci.

The hypotheses which are advanced to explain the relation of rheumatism and old valve lesions to subacute bacterial endocarditis are naturally colored by the views of their authors regarding the etiology of rheumatism. These hypotheses are either mechanical, bacteriological, or immunological and may be summarized as follows:

The *mechanical hypotheses* all assume that the old damage to the valves, rather than the preceding rheumatism, is the important factor in predisposing the heart to reinfection. Rosenow suggests that roughness and calcification of valves predispose to fresh infection but does not explain the mechanism. Schottmüller suggests that the damaged valve acts as an anchoring ground (haftboden) apparently using this term in a mechanical rather than an immunological sense. Babcock thinks that in the damaged valves the phagocytes are less able to reach and destroy attacking bacteria, a bio-mechanical theory. Finally Carey Coombs claims that an attack of rheumatic endocarditis *vascularizes* the affected valve thus increasing the opportunity for bacterial penetration. All of the mechanical processes suggested involve *vascular change*, either a reduction in the number of vessels (Babcock's theory), or an increased number of vessels. (Coombs' theory). It has been quite generally assumed by pathologists that the

valves in healed endocarditis are less vascular than normal. Coombs has examined sections of such valves histologically and claims that they are more vascular than normal. It is evident from his article that he was under the impression, long held, that the heart valves, or at least their distal portions, are normally almost avascular. This has been abundantly disproved but, nevertheless, this question of the increased or decreased vascularity of valves which are the site of healed rheumatic endocarditis cannot be settled until such valves have been investigated by satisfactory methods, such as those used by Bayne-Jones in his study of normal valves. We may sum up the question of the influence of mechanical factors in predisposing damaged valves to further attack by stating that at present our knowledge of the vascularization of such valves is not accurate enough to permit us to draw intelligent conclusions.

From the *bacteriological* point of view the chief hypothesis regarding the relationship between rheumatism and old valve lesions and subacute bacterial endocarditis is the theroy of *latency*. Poynton, who believes that rheumatism is an infection due to the so-called "Micrococus rheumaticus" (Poynton and Paine), also assumes that the original rheumatic endocarditis is due to the same organism. He believes that in endocarditis, just as in the lesions of tuberculosis and syphilis, bacteria may lie latent in an old focus and then, as a result of favoring conditions, take on renewed activity and cause an exacerbation of the process. He therefore regards subacute bacterial endocarditis as the lighting up of a latent lesion rather than a reinfection. From analogy there is no inherent impossibility in this view. It is known that pyococcal infections, osteomyelitis for example, may remain latent for many years and subsequently flare up anew. It is also to be noted that there are very strong resemblances between Poynton and Paine's diplococcus rheumaticus and streptococcus viridans. Rosenow says that differentiation is possible, Major thinks the two organisms are the same. In view of the present confused condition of streptococcus classification one may well hesitate to decide that the two organisms are essentially different. In order to accept the theory of latency however, we must also accept the view that the orginal rheumatic endocarditis was of streptococcal origin, and it is difficult to see why an orginal infection which results in recovery in the vast majority of

cases should, on relapse, result in death in the vast majority of cases. We might assume that all recurrent attacks of rheumatic endocarditis are streptococcal and that subacute endocarditis is merely the severest grade. This is the explanation offered by Reye. Schottmüller, however, expressly states that he has never isolated streptococcus viridans from the blood in cases of rheumatism and it is difficult to explain why, if the organism is never isolated in the orginal attack it should be so frequently isolated in the relapse.

Steinert, Rosenow, Coombs and others have suggested that rheumatism, or a preexisiting streptococcal endocarditis, may in some way *alter the mechansim of immunity*. Steinert dissents from the mechanical explanation of valve reinfection because streptococcus viridans can attack undamaged valves. It would be more correct, perhaps, to say that streptococcus viridans can attack apparently undamaged valves. In the presence of lesions of acute valvular endocarditis it would be hazardous to assert that small foci of old damage, masked by the fresh lesions, could not have been present, particularly as we have shown that many patients with apparently sound hearts who develop subacute bacterial endocarditis have suffered from rheumatic infection. Steinert thinks that the reinfection may be an allergic phenomenon and admits that this presupposes the original endocarditis to have been of streptococcal origin. Rosenow states definitely as a result of his experimental work, that in rabbits that have recovered from infection with his modified pneumococcus[5] the serum loses its power of destroying this germ. Coombs also thinks that rheumatism may reduce the power of resistance to streptococcal invasion.

The question of *local changes in tissue resistance* as a result of bacterial inflammation does not seem to have been seriously considered by writers on the subject. The old work of Cobbett and Melsome certainly suggests possibilities along this line. They showed that rabbits inoculated with streptococci on both ears, after the subsidence of a former streptococcal infection in one ear, showed a more rapid inflammatory reaction in the previously inoculated ear than in the control normal ear, but they noted that the same thing occurred after a chemically produced inflammation. They therefore regarded the phenomenon as non-specific. Nevertheless their work did show that

[5] Probably the same organism others describe as Streptococcus viridans.

previous inflammation could modify subsequent infection unfavorably and for this reason this aspect of the subject seems worthy of further investigation.

BACTERIOLOGY

The exciting causes of the subacute form of bacterial endocarditis may be seen by consulting the following table based on the records of 304 cases. These cases have been selected with care, and the bacteriological records of many undoubted cases have been discarded because it seemed obvious that the technique was faulty and that the organisms described were almost certainly contaminations. In most cases the report covers the bacteriology of the blood obtained during life; in a few instances postmortem results obtained with proper technique have been included.

Organisms isolated from 304 cases of subacute bacterial endocarditis:

	times
Streptococcus	248*
Pneumococcus	16
Bacillus influenzae	16
Staphylococcus	8
Mixed infection	2
Unclassified organisms	7
Meningococcus	1
Micrococcus of Weichselbaum	1
Micrococcus tetragenus septicus	1
Micrococcus flavus	1
Micrococcus zymogens	1
Diplococcus rheumaticus	1
Gonococcus	1

*S. viridans 169 times.

In interpreting these figures it must be borne in mind that many of the records were taken from articles published long before the modern classification of streptococci had been evolved. As Schottmüller, Libman, Horder, Major and others have pointed out, *there are only two organisms concerned with subacute bacterial endocarditis in the great majority of cases*, the so-called streptococcus viridans which causes most of the cases, 95 per cent according to Libman's extensive studies, and the Bacillus influenzae which causes the remaining 5 per cent. These figures are not, of course, mathematically correct, as the table

shows, but for all practical purposes these are the two organisms to be reckoned with. So few other organisms bave been described during the era of modern clinical bacteriology that we are constrained to believe that some, at least, of the older observations concern accidental contaminators or terminal invaders rather than the true cause of the disease.

In order to avoid confusion it is necessary to point out that the organism now known as streptococcus viridans, first accurately described by Schottmüller, appears in the literature under a variety of names. Lenhartz (1901) speaks of it as a small streptococcus or streptococcus parvus. Litten calls if streptococcus gracilis, and Schottmüller described it orginally (1903) as Streptococcus mitior seu viridans. It is probably the same organism as the "Streptococcus der Schleimhauten" of Kruse, Pansini and Pasquale, the saprophytic streptococci (S. salivarius, S. fecaalis) of Horder, Andrewes and Gordon, the modified pneumococcus of Rosenow and the streptococcus tenuens of Hastings. Libman at one time labelled it endocarditis coccus, and in recent years speaks of it as Streptococcus anhemolyticus. Poynton and Paine's diplococcus rheumaticus certainly strongly resembles it.

In view of the confusion which still exists regarding the classification of the streptococci and their differentiation from the pneumococcus group it is not profitable in an article of this scope to enter on a prolonged discussion of this phase of the subject. There are, however, certain peculiarities of streptococcus viridans which may with profit be briefly discussed. In Schottmüller's orginal description of the organism he points out certain facts of importance. The organism grows slowly, the colonies not appearing as a rule until after thirty-six to forty-eight hours. As Libman and Celler pointed out it is necessary to watch the plates for at least six days before discarding the cultures as negative. The growth on blood agar appears as very fine gray to black-green colonies. The organism measures from 0.6 to 1 micron in diameter, usually occurs singly or in pairs, and may occur in short chains. In 1 per cent peptone bouillon long chains may occur. The organism has no capsule, is Gram positive and grows best at a temperature of 37°C. Gelatin cultures may survive for months. The virulence of the organism in animals is very slight. The above description

covers the main points in Schottmüller's original article, since which minor additions to our knowledge of the organism have been made, which, in the main, have little bearing on its recognition. It may be stated, therefore, that the streptococcus viridans constitutes a fairly clean cut type of streptococcus, though occasional cases of subacute endocarditis due to closely allied variants are described.

The *number* of streptococci which may be present in the peripheral blood varies very greatly and apparently bears no definite relation to the severity of the disease. In some patients several cultures must be taken before a positive result is obtained, in others the first culture shows large numbers of organisms. Various authors have described counts of from 1 to 6,500 organisms in 1 cc. of blood, and in some cases the colonies are so numerous as to be uncountable. Assuming that the average volume of the blood during life is about 3000 cc. and that the organism is equally distributed in all parts of the circulation there would be at times from 3,000 to 20,000,000 or more streptococci in the circulation of an infected individual. This leaves little doubt, it would seem, that the organism may multiply in the blood, but it does not clear up the question of whether in subacute bacterial endocarditis the general septicemia is primary or secondary. Harbitz believes from his pathological studies that the valve lesion acts as a distributing focus for the dissemination of the organism rather than representing a local metastasis of a general septicemia. The general course of the disease with its early toxemic symptoms and its late embolic manifestations supports this view.

The data concerning the *immunological reactions* to infection with streptococcus viridans indicate that the organism apparently immunizes itself against the antibodies of the host (Billings, Fox and Lynch). It is relatively resistant to phagocytosis. The organisms in the endocardial vegetations are embedded in thrombotic masses and are resistant to the defensive powers of the blood. The body of the host at times produces complement-fixing antibodies (Kinsella) and at times fails to do so (Fox and Lynch). The bacteriolytic power of the leucocytes and serum is very low. Agglutinating antibodies may be produced by some patients and Fox and Lynch describe the formation of an anaphylatoxin in two cases. Experimental work on immunological methods designed to destroy the organism is not very promising.

SYMPTOMATOLOGY

General considerations

The clinical manifestations of subacute bacterial endocarditis naturally fall into two periods, an early period, when the symptoms and signs are chiefly those of low grade infection, and a late period, when the manifestations of embolism hold the prominent place. The duration of the first period is usually impossible to determine because the onset of the disease is so insidious that the exact time at which infection occurred cannot be fixed. The onset of the stage of embolism is more readily appreciated as the emboli, even when they involve the internal organs, usually give rise to recognizable clinical phenomena. In a few patients, however, there is almost a total lack of recognizable embolic accidents. It is to be noted, too, that concurrent cardiac manifestations due to old valvular disease may mask the new invasion, but this is the case only when the subacute endocarditis attacks patients with marked decompensation. *In the great majority of instances the disease attacks patients with well compensated valvular lesions.*

Before proceeding to a detailed analysis of the symptoms and signs of the disease it is desirable to try to depict a composite picture of the average case. On account of the protean character of the clinical manifestations it is extremely difficult to do this satisfactorily, and yet an attempt is necessary, for no mere presentation of lists of symptoms and signs gives an adequate idea of the condition.

The onset of the disease is usually insidious, and the patient generally consults the physician for loss of strength, lack of endurance or debility. Often there is a history of some loss of weight and perhaps slight fever or chilly sensations. Arthralgias, without obvious redness or swelling of the joints, and fleeting muscle pains are common. Insomnia is quite frequently present, and, as the disease progresses, anorexia and at times active signs of gastric or intestinal irritation may arise. The patient continues to lose strength and weight, a progressive anemia often develops and finally the manifestations of embolism appear. Severe abdominal pain, most often in the left hypochondrium, may occur. Backache with hematuria may be present, or signs of obstruction of one or more peripheral vessels. Meanwhile fever has become

constant, though seldom very high, and may be accompanied by chilly sensations or sweats; emaciation and debility increase, and the patient finally dies at the end of several months of toxemic exhaustion, decompensation, or of some fatal embolic complication such as cerebral softening.

The *signs* which are present are at first slight, except that in a *considerable proportion of the patients there are definite signs of an old valvular lesion.* At first there is little else to be noted, though the patient may show from the onset a change of color ranging from a slight pallor to a definite yellowish tint. As the disease progresses a palpable spleen, bronchitis, an enlarged liver, and finally the varied signs of embolism appear. Petechiae are noted on the conjunctivae, about the axillae, or in some cases widely distributed over the body ; they are apt to occur in crops. Coincident with abdominal pain a sudden enlargement of the spleen with tenderness, or a hematuria with renal tenderness may occur. The patient may develop a hemiplegia or an aphasia, and the urine, which at first was negative or contained only a trace of albumin, begins to show casts of various kinds accompanied by red blood cells and leucocytes. Definite redness and swelling of the joints may occur, tender spots may appear on the fingers or toes, and before death cardiac irregularity, edemas, and signs of decompensation may develop.

The clinical course in *healed* or *healing cases*, as described by Libman, is somewhat different from that which occurs in patients dying with an active infection. Such patients present the picture of chronic endocarditis with fever. The temperature is usually rather low, occasional arthritic and embolic manifestations occur, and the development of a diffuse nephritis with death from uremia is relatively common. Some of these patients show marked "café au lait" pigmentation, develop a marked anemia with weakness and insomnia and die of decompensation.

SYMPTOMS AND SIGNS IN DETAIL

Onset

While it is true that in most cases the onset of subacute bacteria endocarditis is a sneaking one an analysis of 264 cases in which the

method of onset is definitely noted seems to indicate that this feature has been overstressed. In this group 63 per cent gave a history of gradual and 37 per cent of sudden onset. It is necessary to bear in mind that, while pathologically the process is probably always insidious, the clinician bases his judgment on the symptoms and signs exhibited by the patient. In many instances the early stages of the disease appear to be symptomatically latent. This was well brought out by the experiences of the late war which showed that not infrequently men in the preëmbolic stage of the disease carried on, without complaint, full military duty of the most strenuous kind.

In patients in whom the disease runs a clinically insidious course by far the most frequent early complaint is of *weakness*, either alone or accompanied by fever, emaciation, arthralgias or cardiac nervous or digestive disorders. This was the chief complaint in 81 out of the 154 patients with insidious onset. It was not invariably described as weakness but the terms feebleness, asthenia, debility, exhaustion, prostration and malaise were all used to convey the idea. The major complaints which occurred most frequently after weakness were fever, cardiac symptoms (palpitation, dyspnea, cardiac pain) and joint or muscle pains. Digestive disturbances, abdominal pain, headache, nervousness, cough with expectoration and emaciation were each of them the chief complaint in a few patients.

The complaints of the patients in whom the disease begins suddenly fall into three groups: the *febrile group*, in which chills, fever or sweats are the prominent feature; the *arthritic group*, in which painful and often swollen joints dominate the picture: and the *embolic* group, in which, out of a clear sky, the sudden appearence of blindness, hemiplegia, aphasia or acute pulmonary or abdominal symptoms is the first thing that calls attention to the diseased endocardium.

The *puerperal cases* form a separate group for their onset simulates the onset of ordinary puerperal sepsis; only time, the occurrence of positive blood cultures, or the appearance of embolic phenomena makes clear the true nature of these cases.

General nutrition

The *general nutrition* in patients suffering from subacute bacterial endocarditis frequently does not suffer much in the early stages of

the disease, particularly in those cases where the onset is insidious and the appetite is maintained for weeks after the onset. In the cases with acute onset loss of weight is usually a feature from the beginning, especially in those patients in whom the febrile reaction is well marked. In about 10 per cent of all the recorded cases *emaciation* is specifically mentioned as a prominent feature. Some patients, however, remain well nourished up to the time of death, while at the other end of the scale is a small group in whom emaciation is so extreme that they have been spoken of as the *Cachectic type*.

The febrile reaction

Patients with subacute bacterial endocarditis *do not usually run a very high temperature*, though there are a good many exceptions to this rule. Lenhartz states that in the patients with high fever and chills the disease is due to streptococcus vulgaris and not to streptococcus viridans. Schottmüller points out that cases due to streptococcus hemolyticus are apt to have severe febrile reactions. Of 175 patients whose records contained details of the fever only eight had a maximum temperature as high as 105°F., and 34 a maximum temperature as high as 104°F. In four the recorded temperature was never above 99.5°F. In 116 the daily maximum was 103°F. Of 128 patients whose temperature range is recorded the daily variation did not exceed 4° in 96. Ordinarily then, the daily range does not exceed 4° and the maximum temperature does not exceed 103°F.

The fever is accompanied in certain patients by *chills*, in others by *sweats* and in still others *chill, fever and sweat* occur in regular sequence. Of 249 patients whose records contain details, 116 are noted to have fever only, 70 fever and chills, 16 fever and sweats, and 34 fever, chills and sweats. The chills may be occasional or may be so regular and constant as to raise the suspicion of malaria, these cases constituting the so-called *pseudo-malarial type* of the disease. In such patients a daily range of 9° may occasionally be noted. The sweats may be slight or profuse, may occur only occasionally, or may be frequent and occur mainly at night leading to a suspicion of pulmonary tuberculosis.

Some patients are stated to be *afebrile*. French writers particularly have referred to this type, but Debré seriously doubts the existence of such cases and states that in his opinion they would not be described if the temperature was taken at more frequent intervals. There is no question that certain of the more prolonged cases have long periods of apyrexia, and many patients have short afebrile periods, but it is doubtful whether any patient runs the entire course of the disease without at some time having fever. It is not infrequent for the fever to be higher at the height of the disease than it is toward the close, and if patients are seen only in the later stages erroneous conclusions may easily be drawn.

Cardiac manifestations

Inasmuch as a considerable proportion of the patients have old cardiac lesions, either fully compensated or in various stages of subcompensation or decompensation, cardiac symptoms are a frequent accompaniment of subacute endocarditis. The reinfection undoubtedly may increase existing cardiac symptoms or produce symptoms where none were formerly present, but it is often exceedingly difficult to decide on the relative importance of the old and fresh lesions so far as the production of symptoms is concerned. *Dyspnea* is the most common cardiac symptom, occurring in over a third of the patients, and ranging in severity from slight breathlessness on exertion to the severest grade of orthopnea. It may be constant or paroxysmal and often occurs quite early in the disease. *Palpitation* is another frequent symptom and occurs in about one fourth of the patients. It also may rarely be paroxysmal. *Cardiac pain* is noted in about 12 per cent of the cases, varying from a slight sense of oppression to definite and severe anginal attacks. In a few cases it is associated with embolism of a coronary artery.

Some idea of the character of the heart lesions to be expected may be gathered by consulting the table under pathology on page 112. A comparison of the lesions revealed at autopsy with those diagnosed clinically is shown in the following table based on 146 pathological and 271 clinical records:

	PATHOLOGICAL		CLINICAL	
	per cent		*per cent*	
Mitral disease	39	88.1	49.7	96.5
Aortic disease	10.8		18.4	
Mitral and aortic disease	38.3		28.4	
Pulmonary valve disease	2.7		1.1	
Tricuspid valve disease	2.0		0.7	
Mitral and tricuspid disease	0.6		0.3	
Aortic and tricuspid disease	2.0		0.0	
Aortic and pulmonic disease	0.6		0.3	
Mitral, aortic and tricuspid disease	2.7		1.1	

The comparison of clinical and pathological data naturally shows some discrepancies. These are to be expected for two chief reasons; lesions noted at autopsy are often so slight that they entirely fail to produce clinical signs, and the interpretation of cardiac murmurs is far from being an exact science. It is to be noted that the lesions most often missed clinically are the less common ones which are difficult of diagnosis. The *heart signs* to be expected in cases of subacute bacterial endocarditis are, therefore, usually those of mitral or aortic disease often associated with overaction on account of the fresh infection.

Two special points of interest in connection with the cardiac signs must be considered: (1) What change in the preexisting signs results from the fresh infection of a previously damaged valve, and (2) how often are murmurs entirely absent?

We have already pointed out in discussing the pathology of the disease that the location and character of the newly formed vegetations is sometimes such that *no change in the preëxisting cardiac murmur or murmurs results*. This is not usually the case however, for large thrombotic masses often occur and a gradual intensification of or change in the quality of the murmur results. Not infrequently new valves are involved and this leads to the development of recognizable murmurs not previously present. The formation of large *areas of vegetation on the wall of the left auricle* may also cause definite and very loud murmurs. In two patients observed by the author harsh systolic bruits in the pulmonic area were associated with this change. *Rupture of a chorda tendinea* may at times, but not necessarily,

cause the sudden appearance of a vibrant murmur or an audible snapping first sound (Palfrey), and the *tearing or perforation of a valve sail* may have a like effect. Particularly in the late stages of the disease definite changes in the original murmurs may therefore be expected in a considerable proportion of the cases.

Among 279 case records analyzed there were 5 in *which no murmurs were present* during life, but 2 of these were patients with mural lesions in the pulmonary artery. In the cases of Capes and Dickson and Wilbur autopsies showed quite extensive formation of vegetations but these were flattened and so situated that they did not interfere with the competency of the valves. Capes' patient was under observation for a long time and at least five competent observers passed on the physical findings in the heart. In the case of Dolard and Porot, which lasted six months, a murmur was noted on only one occasion. It is evident therefore that there are occasional cases, perhaps 1 per cent of the total number, in which definite murmurs cannot be made out.

The character of *the pulse* naturally varies with the type of cardiac lesion but inasmuch as the old valve lesion, when present, is nearly always left sided the Corrigan pulse or the pulse of mitral disease are the types most frequently encountered. The infection or reinfection of the valve does not as a rule greatly modify either the quality or the rate of the pulse until rather late in the disease. Where the pulse is recorded it is seldom that it is above 120 until the end is near and irregularities are decidedly infrequent. In 301 case records, *irregularity* (without classification) is mentioned 9 times, *auricular fibrillation* 4 times and *auricular flutter and gallop rhythm* each once. These figures are, however, probably misleading for many of the cases were recorded long before modern methods of pulse study were in vogue.

Involvement of the air passages

Involvement of the lower air passages is common in subacute bacterial endocarditis while the upper air passages are seldom involved. An occasional mention is made of *coryza*, and there is one case on record in which *edema of the glottis* occurred. *Epistaxis* is not infrequent On the other hand *cough* is a very common symptom. In the early

stages of the disease it is often dry and unproductive but in a good many patients a definite *bronchitis* occurs and may be one of the earliest manifestations. In the later stages *hemoptysis* with *pleurisy* and the signs of *localized consolidation* are not infrequent, and are associated with pulmonary infarction. *Hydrothorax* occurs not infrequently and signs of *hypostatic congestion* at the bases are quite common. *Lobar pneumonia* occurs occasionally and may be the immediate cause of death. A few cases terminate with a sudden *acute pulmonary edema*. *Broncho-pneumonia* is very common on the autopsy table and not infrequently diagnosed during life. *Pulmonary tuberculosis* is an occasional accidental complication. The *respiration* is seldom markedly influenced during the course of the disease unless some pulmonary complication is present except in the pseudo-malarial cases when it may become rapid at the time of the chill. In the average case the respirations range between 20 and 30.

Gastro-intestinal manifestations

By far the most common gastro-intestinal manifestation is *anorexia*. This is exceedingly common, often an early symptom, and may be the first indication of ill health. Gastric distress with nausea and occasional *vomiting* attacks are not infrequent during the embolic period. The vomiting is in some instances associated with cerebral embolism. *Diarrhea* also occurs not infrequently and may be paroxysmal and associated with fetid stools and even with melena. There is a strong suggestion in some cases that showers of intestinal emboli may produce this manifestation. Nicholl states that blood in the feces is common. *Constipation* is not infrequent and *flatulence* may be a prominent feature.

The *tongue* is usually slightly coated but may be clean. At times it is dry and brown, the tongue of toxemia. It may be over red and glazed and is occasionally described as denuded. The *teeth* are not infrequently noted to be diseased, pyorrhoea, caries and root abscesses being the lesions commonly noted. The *tonsils* are more frequently described as normal than as abnormal, but congestion, hypertrophy and the presence of exudate in the crypts is described in some cases. Bleeding from the gums is occasionally noted. *Parotitis* and *otitis media* are rare complications. The *liver* is frequently not enlarged,

but in many cases is enlarged, hard and tender from chronic passive congestion. *Cholecystitis* rarely occurs as a complication and *jaundice* is only occasionally noted.

Haematopoietic system

Changes in the blood-forming organs undoubtedly occur in most patients with subacute bacterial endocarditis and are reflected in the peripheral blood. The number of blood counts actually recorded in the literature is comparatively small as they are entirely lacking in many of the older papers. In 94 recorded counts *the red cells* were below 3,000,000 per cubic millimeter in approximately one-third, below 4,000,000 per cubic millimeter in approximately another third, and between 4,000,000 and 6,000,000 in the remaining third. In only 8 records was the red count less than 2,000,000 and in only 7 over 5,000,000. Of 104 *hemoglobin* estimations 72, or roughly two-thirds, showed between 50 and 70 per cent. The *color index* was usually less than one, but occasionally more; in a few instances a chlorotic type of anemia was present. In the patients with the more pronounced anemias deformity of the reds, polychromasia, macrocytes, and nucleated reds were at times noted. So few platelet counts are on record that no definite conclusions can be drawn as to their behavior in this disease.

The *leucocytes* show great variation in different patients and in different stages of the disease. There is no uniformity in their behavior. Cotton gives the average leucocyte count as 10,800. In 40 per cent of the recorded counts 10,000 per cubic millimeter was not exceeded, in the remaining 60 per cent counts of from 11,000 to 55,000 leucocytes per cubic millimeter are noted. There are few counts below 5000 and equally few above 30,000. The differential counts also vary greatly in different patients. The polymorphonuclear counts range from 26 per cent to 89 per cent; the mononuclears (large and small) from 11 to 58 per cent. Eosinophiles are frequently absent and when present seldom exceed 2 per cent; in one of Freyer's patients, however, 35 per cent of eosinophiles was present on one occasion. Basophiles are hardly ever recorded. Myelocytes, usually neutrophilic, occur in a few cases in small numbers as Vaquez noted. Not over 2 per cent are recorded in any available record. The leuco-

cyte count may progressively decline as the disease progresses but in some instances a gradual increase in the leucocytes is observed. In some of the author's cases a series of leucocyte counts showed a progressive decline in numbers with a progressive increase in polynuclears, in others the differential count remained about the same over long periods irrespective of the changes in the total count. There is little in the literature on the *blood chemistry* though Cain and Paraf report one patient with a decided increase in blood urea.

We may summarize this aspect of the disease by stating that as a rule there is a moderate grade of anemia, usually of the secondary type, which may be accompanied by either a progressive increase or a progressive decrease in the number of leucocytes and by either a polynucleosis or a mononucleosis. As contrasted with other pyococcal infections a considerable proportion of the patients show a lack of leucocytosis.

There are two groups of cases which occur rather rarely that demand special mention: (1) the so-called *anemic type* and (2) the so-called *splenomegalic type*.

In the *anemic type*, the importance of which has been emphasized by Achard and Foix, the anemia is the outstanding feature, and if the cardiac signs are inconclusive they are apt to be mistaken for evidences of anemia rather than endocarditis and the case may be mistaken for one of latent malignancy, tuberculosis or primary anemia. The red blood count in such cases may be below 2,000,000 cells per cubic millimeter, but in some of the most pronounced cases on record the leucocyte count was quite high and the differential count showed a high polynuclear index.

The *splenomegalic type*, which simulates splenic anemia, was first recorded by Samuel West in 1896, but we are indebted to Parkes Weber for calling attention to it. Osler, Riesman, Jochmann and Auerbach have all recorded cases. In these patients weakness, pallor, marked splenomegaly and fever are the prominent features. The blood picture is at times very suggestive of splenic anemia but in some patients this is not the case. In Weber's case the red blood cells ranged from 5,625,000 to 3,260,000, the leucocytes from 2840 to 1360, and the polymorphonuclears varied between 26 and 28 per cent. In Osler's patient the red count was 2,700,000, the leucocytes numbered 8000

and the polynuclears were 40 per cent. In Auerbach's patient the red count was 2,700,000, the leucocyte count 3300 and there were 47 per cent polynuclears, 45 per cent mononuclears and 7 per cent eosinophiles. In West's case, on the contrary, the leucocyte count ranged between 50,000 and 75,000 and in Riesman's case while there were only 4450 luecocytes 80 per cent of them were polynuclears. Usually, too, even when the cardiac signs are inconclusive, some of the other evidences of endocarditis are present, arthritis, skin manifestations, embolic aneurism, etc.

The changes in the *spleen* may properly be considered under this section. In the records of 289 cases the organ is noted to have been enlarged in 163 or 56 per cent. However, in 69 of the records no mention of the organ is made so that of the patients whose records contain definite mention of the condition of this organ 74 per cent showed enlargement. In a few instances the organ is described as being enlarged to percussion, but in most cases it was palpable. There is therefore clearly demonstrable enlargement of the organ in a considerable proportion of the patients. This varies from bare palpability to enormous enlargement, as big as a leukemic spleen, in the splenomegalic type. The splenic enlargement is not infrequently demonstrable quite early in the disease, is apt to progress intermittently as a result of infarction, and is frequently associated with left hypochrondriac pain, marked tenderness on palpation and at times a perisplenitis with an audible friction rub. Definite clinical signs suggesting infarction occur in 47 per cent of the patients. In one case personally observed the spleen while palpable never seemed large but the patient suddenly developed lower left thoracic pain with dullness and bronchial breathing at the base of the left lung which persisted for weeks and was not accompanied by rales. The condition was regarded clinically as pulmonary infarct but the autopsy showed only atalectasis from the compression of the lung by an enormous infarct in a highly placed greatly enlarged spleen.

Very little is said in the published reports regarding changes in the *lymph nodes*. General glandular enlargement is occasionally noted and is usually stated to be slight. Regional nodes such as the cervical, submaxillary, and inguinal are noted to be slightly enlarged in a few instances. It is evident that marked reactive changes in the lymph nodes are uncommon in this condition.

Cutaneous manifestations

The *general coloring* of the skin in subacute bacterial endocarditis varies in different patients and at different stages of the disease. As a rule there is an increasing pallor, slight at first, and in the more protracted cases often associated with pigmentation late in the disease. Most commonly the patients are simply described as "pale," "very pale" or "anemic looking," but quite frequently the pallor is described as "yellowish," "sallow," "greenish," "waxy," "earthy" or "leaden." On account of the associated old valvular lesion many of the patients show a combination of pallor and cyanosis. At times the patient is described as "flushed" or as having a "typhoid facies." Rather rarely the skin is said to be "subicteric" or "icteric."

Pigmentation is not at all uncommon in the more chronic cases; it is generally most marked about the face, is occasionally patchy simulating the pigmentation of pregnancy, but more often a fairly diffuse yellowish-brown color which Libman has well characterized as the "café au lait" tint. It may occur in the extremities only, as in Weber's splenomegalic patient.

The *skin eruptions* which occur in subacute endocarditis are of great diagnostic importance and exhibit considerable diversity. The most common lesions are the *petechiae* which occur on the mucous membranes or skin in the majority of cases at some period of the disease. They are apt to appear in crops and are presumably embolic in origin as they not infrequently occur synchronously with some gross embolic insult such as a cerebral or splenic embolism. They are often overlooked, being noted in only 38 per cent of the case records. In many patients they must be carefully sought for as they are small in size and few in number. The palpebral conjunctivae, the axillary regions, the base of the neck and the clavicular regions should be carefully scrutinized. The lesions are intracutaneous hemorrhages, usually 1 to $1\frac{1}{2}$ millimeters in diameter, not elevated and not disappearing on pressure. They frequently have a white or yellowish center pin point in size. They are not to be confounded with the common small skin angiomata. These are elevated above the skin level, distinctly cerise in color and may or may not disappear on pressure. In some patients the skin hemorrhages are larger and more accurately described as

purpuric, and in a few instances *sugillations* have been described. As Rapin has pointed out the skin lesions are sometimes painful.

Skin eruptions which are non-hemorrhagic in character are not common but are not exceedingly rare. *Erythema* is the most frequent of these. It may be of the simple variety but occasionally *erythema multiforme* and *erythema nodosum* have been noted. Debré has described a case with large painful erythematous plaques. *Dermatographia and urticaria* have been occasionally noted. Patches of skin *gangrene* are sometimes seen, and in the terminal stages of the disease *decubitus* is not uncommon. *Herpes labialis* is of rather rare occurrence.

The skin lesions in connection with the fingers and toes are important enough to demand special attention. While they were noted by Rapin, Heubner and Münzer, it was Osler who called attention to the great importance of a certain type of lesion usually occurring on the extremities and now frequently referred to as Osler's sign. Osler describes the lesions as an *ephemeral painful nodular erythema*. The French clinicians speak of the sign as "faux panaris" or "signe des doigts." The lesions are rarely seen except on the fingers and toes. They are usually from 1 to $1\frac{1}{2}$ centimeters in diameter, red, slightly elevated, often pale in the center and generally disappear at the end of a few hours. They appear in crops and usually involve the pads or sides of the digits. Osler found them in 7 of his 10 cases published in 1908 but this is certainly a much higher proportion than is found in the cases recorded in the literature. The smaller lesions are intracutaneous but the larger ones, as Parkes Weber has pointed out, are subcutaneous. Nicholl states that they occasionally suppurate and leave a small ulcer.

There are two other types of finger or toe lesions which occasionally occur: (1) *Tender fingers or tender toes* similar to those occasionally seen in typhoid fever, and (2) curious *subungual linear hemorrhages* which look exactly like a splinter under the nail. I have seen these in but one patient and can find no reference to exactly similar cases though Horder describes a vivid linear splash at the side of the nail bed and Lerebollet and Mouzon speak of subungual ecchymoses.

While not strictly a skin lesion it is advisable to call attention here to the importance of *clubbing of the digits* in this disease. In recent

years the English School of Clinicians has laid considerable stress on this sign and regard it as evidence of an infectious process. I have noted it in several cases and in one patient observed its gradual development during the course of the disease.

Vascular lesions

The occurrence of *embolism* in large peripheral vessels is not a very uncommon event in the course of subacute bacterial endocarditis. The following table shows the frequency and situation of the lesion as observed in 300 patients:

	times
Embolism of radial artery	7
Embolism of a foot artery	6
Embolism of brachial artery	5
Embolism of popliteal artery	2
Embolism of nasal artery	2
Embolism of a leg artery	2
Embolism of internal carotid	1
Embolism of aorta	1
Embolism of ulnar	1
Embolism of axillary	1
Embolism of mesenteric artery	1

This indicates that peripheral arterial embolism is clinically manifest in 9 per cent of the cases. In the same group of patients there were two with symptoms diagnosed as coronary embolism, two with pulmonary emboli in large branches and two with thrombosis of the femoral vein.

The occurrence of clinically appreciable *embolic aneurysms* is not frequent as these are most common in the vessels of the internal organs. In the 300 case records there are 2 instances of femoral aneurysm which were recognizable during the life of the patient, one reported by Osler, the other by Denechau and Picard. Recently Richey and MacLachlan have reported a case in which an aneurysm of the posterior tibial was palpable during life. Their article and that of Huchard and Bergouignan give a good review of this phase of the subject. The vascular lesions in the internal organs are best considered under visceral lesions.

The nervous system

Symptoms referable to the nervous system are of frequent occurrence in subacute bacterial endocarditis. *Headache* is the most common symptom. It may occur early as a result of the toxemia or may not appear until the embolic period when it may be associated with cerebral embolism or rarely with meningitis. At times it is the earliest symptom noted and it may be intense. Usually it is described as general but it may be frontal, vertical or occipital. *Vertigo and tinnitus* occasionally occur. *Insomnia* is a relatively frequent symptom and may be pronounced and distressing. *Irritability* or *excessive nervousness* is noted in many of the records. Generalized *nerve tenderness* is seen occasionally. *Delirium* is not common and when it does occur is usually a terminal manifestation. Toward the end of the disease *convulsive seizures* described as "eclamptic" or "epileptiform" are occasionally noted and *somnolence* or *apathy* gradually deepening into *coma* is not very rare as a terminal event. In Scheidemantel's case extreme *drowsiness* was a comparatively early phenomenon. *Sciatica* is occasionally noted.

The *mental status* of these patients is frequently commented upon and it is quite generally agreed that a condition of *euphoria* is exceedingly common. In some patients, however, *depression* and even *melancholia* has been observed, and in rare cases *pseudomania* or an *acute psychosis* develops. Definite inflammatory processes such as *meningitis* are unusual as contrasted with their frequency in acute pneumococcus endocarditis. The streptococcus viridans has occasionally been isolated from the spinal fluid obtained by lumbar puncture.

The frequency of clinically appreciable *focal lesions* in the central nervous system due to embolism or hemorrhage is shown by the following table covering 300 records:

	times
Right sided hemiplegia	16
Right sided hemiplegia with aphasia	13
Left sided hemiplegia	17
Left sided hemiplegia with aphasia	1
Hemiplegia (side not noted)	8
Diplegia	2
Aphasia	3
Crossed paralysis, hemianaesthesia and hemianopsia, each	1

This table shows that hemiplegia, diplegia or aphasia occurred in just 20 per cent of the patients. The aphasia was usually associated with right hemiplegia but occurred alone in 1 per cent of the patients.

The few cases in which the symptoms concerned the nervous system predominantly, the so-called "*nervous type*" of the disease need special mention. In Claude's patient, a boy of eighteen who had severe chorea six months before the onset of the endocarditis, there were marked meningeal symptoms with a spinal fluid showing albuminosis and containing at first polynuclear and later mononuclear cells. These symptoms were followed by right hemiplegia and alternating facial paralysis. Death occurred from cachexia after a remission of the nervous symptoms lasting twelve days. The autopsy showed a slight meningitis of the cerebral cortex with an area of softening in the left pedunculo-protuberential area associated with an arteritis of the basilar artery.

In the patient of H. and F. Lewy, the disease began with incontinence and terminated after eighteen months in an attack of unconsciousness followed by paraplegia. There were areas of superficial necrosis, which later became ulcers, on both legs. The autopsy showed meningomyelitic areas in the first and second dorsal segments with old and fresh aortic endocarditis and some arteriosclerosis. In both of these patients cardiac murmurs, and other evidences of endocarditis were present but the neurological lesions were the striking ones.

Genito-urinary manifestations

It was pointed out under the head of pathology that a peculiar form of *nephritis* is of common occurrence in subacute bacterial endocarditis. Long before the nature of this lesion was recognized it was noted that the more prolonged forms of endocarditis were often associated with clinical changes suggestive of renal disease. *These changes usually manifest themselves in the urine only.* The occurrence of clinical symptoms definitely referable to nephritis is unusual and generally means that a superadded diffuse nephropathy is present. Only occasionally therefore, and particularly in the bacteria free stage, may we expect to find the renal type of edema, hypertension, cardiovascular changes and uremia.

I have been able to find 196 records of *urine* examinations in the literature or in personally observed patients. The following table shows the findings in brief form:

	times
Normal urine	24
Albuminuria	42
Albumin and casts	33
Albumin and red blood cells	20
Albumin and red and white cells	3
Albumin, casts and leucocytes	13
Albumin, casts and red blood cells	25
Albumin, casts and red and white blood cells	20
Nephritis (without details of urine)	6
Casts without albumin	1
Leucocytes only	2
Red blood cells only	1

The significance of these findings cannot be accurately gauged without taking into account the fact that the observations are often single ones made at all stages of the disease, and that quite different results might be recorded if a series of examinations were made in every case. The urine is not infrequently normal in the early stages of the disease but is nearly always definitely pathological in the later stages.

So far as evidence of *nephritis* is concerned it is to be noted that the amount of albumin recorded varies all the way from a very faint trace to five pro mille on the Esbach scale. The casts described are usually hyaline or granular. Blood casts are not very uncommon; pus casts, epithelial casts, fatty casts and waxy casts are rarely encountered. The blood present may be microscopic in quantity or markedly bloody urine may occur. Marked pyuria is decidedly infrequent. Very few records of kidney function are to be found, but figures varying from 11 per cent elimination of phthalein in two hours to normal are noted in the few cases tested.

In addition to signs of nephritis the urine in a good many patients shows a well marked *diazo reaction*. This is of no particular significance except in the question of differential diagnosis. Naturally, too, as some patients are subicteric or icteric, *urobilin* and *bile* are occasionally found in the urine.

About one-third of the patients show clinical evidences of *renal infarction.* The renal infarcts may be painless and attention may be called to them by the sudden occurrence of hematuria, but in many patients lumbar pain, backache or generalized abdominal pain precede or accompany this. *Ureteral colic* from the passage of clots and even *retention* from coagulated blood have been known to occur. Frequency, nocturia, and various degrees of dysuria are not uncommon.

Symptoms or signs referable to the genital organs are decidedly unusual in the male. In the female *amenorrhea* is not at all uncommon and *metrorrhagia* occasionally occurs. In the puerperal cases the onset is with the symptoms and signs of *puerperal sepsis.*

Bone, joint and muscle manifestations

Pain and swelling of the joints is a common feature in subacute bacterial endocarditis. The degree and extent of joint involvement varies greatly in different patients and at different stages of the disease. The joint involvement may take the form of *arthralgia,* of *acute arthritis* or of *chronic anchylosing arthritis.* Fleeting joint pains, often accompanied by stiffness of the joints, and muscle pains, are very common in all stages of the disease, more common in the early than the late stages. Such pains may be an early symptom, in fact the earliest one in some patients. Acute *arthritis* with pain, redness and swelling is also common and in some patients is the outstanding feature of the disease. At times it involves single joints, particularly the knees, in other cases it is polyarticular. The joints of the lower extremities, particularly the knee and foot joints, are involved three times as often as those of the upper extremities. Where the arthritis is an early manifestation it may disappear as the disease progresses. Occasionally streptococcus viridans has been isolated from the joint effusion. Rarely, as in the case reported by Debat-Ponsan, *a chronic progressive anchylosing arthritis occurs.*

Changes in the periosteum and bones are rarely noted. In one patient *periostitis* of the frontal bone is recorded. Attention should be called here to *sternal tenderness* a sign which was first described by Libman. It is noted in the literature only a few times but inasmuch as it is not a very obvious sign and could easily be overlooked

the number of cases reported is probably not a true index of its frequency. The writer has looked for it in subacute endocarditis for a number of years and has found it in only a small proportion of the patients.

Myalgia either alone or as an accompaniment of arthralgia or arthritis is of frequent occurrence particularly in the early stages of the disease. In rare cases progressive changes in the muscles with marked atrophy have been noted. Persistent *lumbago* occurs in a small percentage of the patients.

Ocular manifestations

The *ocular manifestations* of subacute bacterial endocarditis are of considerable importance and have been discussed in some detail by Falconer and by Dellmann. There is little doubt that the reference to eye changes in the literature gives an entirely false impression of their frequency. *Retinal changes* are noted in about 10 per cent of the published records of patients in whom ordinary clinical examinations were carried out. Falconer, who specially examined the eye lesions in 15 patients, found changes in the eyes of one-third of them. Such changes as occur are nearly all retinal, as the suppurative panophthalmitis which may result from generalized sepsis with more virulent organisms is very uncommon in subacute bacterial endocarditis.

Embolism of the central artery of the retina or its larger branches with *sudden blindness* occurs in about 2.5 per cent of the recorded cases and is occasionally bilateral, as in the patient of Mohr and Böhm. Small retinal hemorrhages are much more common, occurring according to the records in about 6 per cent of the patients, this figure undoubtedly being much too low. Optic *neuritis* or *neuroretinitis*, which may progress to the stage of *optic atrophy* is recorded in 3 per cent of the case reports, but if Falconer's experience is trustworthy probably occurs much more frequently than this. None of Falconer's 5 patients admitted any failure of vision and this lack of subjective symptoms referable to the eyes doubtless accounts for the fact that more eyeground examinations have not been recorded.

According to Dellmann ophthalmologists have recognized two types of septic eye changes, *metastatic ophthalmia*, a supposedly embolic lesion involving the retina primarily, and *retinitis septica* characterized

by round or oval hemorrhages and miliary white foci assumed to be of toxic origin. In subacute bacterial endocarditis both types of lesions occur and we have in addition optic neuritis which Falconer regards as toxic. The hemorrhagic lesions of the retina, like those on the skin, occur in crops and, while the hemorrhages sometimes leave behind patches of exudate, many of them, according to Falconer, leave little or no trace behind. The frequency of ocular lesions emphasizes the importance of routine examinations of the fundus in doubtful cases. The occurrence of retinal lesions may indicate a serious condition where the general physical examination showed only dubious signs.

COURSE, DURATION AND TERMINATION

The *course* of subacute bacterial endocarditis is usually not progressively downward. There are frequently remissions, when the fever diminishes or even disappears for days or even weeks, and exacerbations which in the early stages are perhaps due to fresh invasion of the blood by streptococci and in the late stages are due to the effects of emboli or to secondary infections. The remissions are at times very deceptive, for, with few exceptions the disease finally terminates fatally.

The *duration* of the disease varies within wide limits, the variation depending on the virulence of the organism, the resistance of the individual, the occurrence or lack of occurrence of embolism of important vessels, the condition of the heart muscle, and the development of secondary infection. Analysis of 281 records in which the duration of the disease is stated shows that death occurred between the end of the third and the end of the eighth month in 212 patients or 75 per cent. Only 9 patients lived over sixteen months, though 6 of these lived over two years. The largest number, 63, died during the course of the fifth month. It is, of course, understood that these figures are not absolutely accurate because they are based on clinical symptoms and the disease is frequently latent in the early stages. It is also to be noted that a patient may be suddenly cut off by a terminal infection or pulmonary edema before the third month, these cases constituting the so-called "shortened form" ("forme raccourcie" of French authors).

The *cause of death* in subacute bacterial endocarditis is frequently not stated in the records and is by no means easy to decide from the autopsy protocols in many cases. The following table indicates the assigned or probable causes of death in 193 patients:

Assigned causes of death

Cachexia or exhaustion (toxemia)		61
Cardiac insufficiency:		
Acute	8	
Chronic	48	56
Embolism:		
Cerebral	44	
Pulmonary	4	
Coronary	1	49
		166*
Terminal infections:		
Pneumonia	5	
Peritonitis	2	
Erysipelas	1	
General	2	
Meningitis	2	12
Terminal edema:		
Lungs, acute	3	
Glottis, acute	2	5
Sudden death		4
Uremia		4
Anemia, severe		2
		193

*Or 86 per cent

In commenting on this table it is necessary to point out that the terms *cachexia* and *exhaustion* are rather vague, and yet probably an even larger percentage of patients than the table indicates die "by inches" so to speak. In most of these patients we are doubtless dealing with a gradual decline resulting from the *toxemia* with the deficient nutrition and gradual cardiac deterioration which accompanies this. In most of these patients cardiac failure is the immediate cause of death though the ordinary signs of decompensation are lacking. The frequency of *cardiac decompensation* as a cause of death is

readily understood as so many of these patients are already suffering from valvular disease with subcompensation or lessened cardiac reserve power. The frequent occurrence of *embolism* as a cause of death hardly needs comment in view of the pathology of the disease. Toxemia, decompensation and embolism are responsible for 86 per cent of the deaths, the other factors being of much less frequent occurrence as the table shows.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In his Gulstonian Lectures, Osler indicates the difficulty of diagnosing endocarditis and the reasons therefore in the following sentence: "The protean character of the malady, the latency of the cardiac symptoms, and the close simulation of other disorders combine to render the detection peculiarly difficult." While these remarks refer to infectious endocarditis of all types they are applicable to the particular form under discussion. The protean character of the subacute form of the disease is indicated by the many sub-types which are described in the literature. Debré in his critical review speaks of the following forms:

1. The apyretic form the existence of which is doubtful.
2. The anemic form, simulating primary or secondary anemia.
3. The hemorrhagic form, simulating splenic anemia and perhaps better called the *splenomegalic* form as hemorrhages are not always a prominent feature.
4. The pseudomalarial form.
5. The painful form, in which multiple painful peripheral emboli dominate the picture.
6. The nervous form, with meningeal or spinal symptoms.
7. The silent form, in which a heart murmur is absent.
8. The forme fruste, in which the disease is latent and is revealed by a sudden cerebral accident.
9. The rheumatic form.
10. The psychic form.

Other forms could be logically created, such as the cachectic form, and the renal form, but Debré's list suffices to indicate the great variability of the symptomatology.

As Debré points out diagnosis is difficult because of the extremely insidious onset of the disease, the preexistence of an old heart lesion in many patients, and the lack of specificity of the signs over long periods of time. The embolic features, which are most important in leading to the suspicion of endocardial disease, are usually late phenomena. We can hardly follow Dickson and Wilbur in regarding petechiae or Osler's nodes as early signs.

No one has discussed the diagnosis more clearly than Osler and as he points out the cardinal diagnostic features in most patients are *fever, the existence of an old valve lesion, embolic phenomena, and positive blood cultures.*

Fever is the dominant feature in most cases and is probably always present at some period of the disease. The presence of an *old valve lesion* is to be expected in a considerable proportion of the patients. It is important to remember that in the early stages no modification of the old murmur may be present though, as the disease progresses, changes in the signs usually occur. Of the *embolic phenomena* the *petechiae* are the most important. They appear in crops but are often few in number and should be carefully sought for especially on the palpebral conjunctiva and about the neck and axillary regions. The *ephemeral nodular erythema* of the extremities (Osler's sign) is of great importance when present, and retinal hemorrhages and other ocular changes should always be sought for. *Pain in the splenic region* with an enlarged tender spleen, abdominal pain with *hematuria* and signs of cerebral embolism are also of great importance though usually late phenomena. *A palpable spleen* occurs in a considerable proportion of all patients and may be a comparatively early sign. A *positive blood culture* is of course, the most important diagnostic sign but it is to be remembered that several cultures may be necessary before positive results are obtained and that a series of negative cultures does not exclude the diagnosis of subacute bacterial endocarditis especially when the disease is in the bacteria-free stage described by Libman. In some cases *urinary cultures* may be of value as Dickson and Wilbur and Gow have shown. If *subcutaneous abscesses* develop cultures from them may reveal the organism. Gow suggests cultures from blood obtained by *splenic puncture* but it is questionable whether this is a justifiable procedure as spontaneous rupture of infarcts has

caused fatal peritonitis and the chances of injury by the needle are not inconsiderable. Other signs of importance in diagnosis are the *color* of the patient (pallor or café au lait pigmentation), the frequent *arthritic manifestations*, *clubbing of the fingers*, *a progressive anemia*, *urinary changes*, particularly albuminuria with casts and blood, and in some patients *sternal tenderness* or *chronic purpura* of the lower extremities.

In patients with *advanced decompensation* whose valves become reinfected the ordinary signs are often completely lacking as has been pointed out by Steinert, Rosenow, and particularly by Lutembacher. According to the last named author the signs suggesting reinfection in these patients are the appearance of the evidences of infarction, an aggravation of the decompensation and a failure of cardiac remedies, digitalis for example, to produce their usual results.

Differential diagnosis

The great number of conditions with which subacute bacterial endocarditis has been confused again emphasizes the protean symptomatology. In the early stages of the disease a diagnosis of *neurasthenia* is frequently made as the chief complaint is lassitude or weakness and the importance of the presence of an old valvular lesion is frequently overlooked, particularly if the examining physician has been aware of it for years. In cases with a febrile onset a severe *coryza or influenza* may be diagnosed at first. As the disease progresses and *fever* dominates the picture a diagnosis of *malaria*, or *typhoid fever* is frequently made, especially if the heart signs are inconclusive. During this period *pulmonary tuberculosis* is frequently suspected and some patients are sent to tuberculosis sanatoria. In Europe *malta fever* or *trench fever* may be suspected. *Pyemia* without endocarditis may be diagnosed, or a *hidden focus of pus*, a *pylephlebitis*, *genitourinary tuberculosis*, *an abscess of the spleen*, *liver*, *or kidney or a pelvic peritonitis* may be thought to exist. The progressive *blood changes* may lead to the suspicion of *occult malignancy* with secondary anemia, or to the diagnosis of *pernicious anemia*. When the splenic enlargement is very marked *splenic anemia* may be suspected. Rarely *brain abscess or brain tumor* is simulated. During the embolic stage a painful abdominal attack may lead to the diagnosis of *appendicitis or gall stone colic*.

The most difficult cases to differentiate are those in which *a marked arthritis* is an early feature, and cases of *chronic endocarditis* with fever not associated with a general infection. The arthritic cases are, of course, mistaken for *acute or subacute articular rheumatism*, a mistake which is easily understood as so large a proportion of the patients have already suffered from this disease. Furthermore as Schürer has shown an arthritis due to infection with streptococcus viridans but without endocarditis may occur. Schürer calls these cases "septic rhematoid." The cases of chronic endocarditis with fever can only be differentiated by prolonged observation and repeated blood cultures.

A diagnosis of *neurasthenia, coryza or influenza* is likely to be made in only the early stages of subacute endocarditis and is soon disproved by the clinical course of the case. *Malaria* is easily ruled out by a blood examination and the failure of the condition to react to specific medication. *Typhoid fever* can be eliminated by the Widal reaction, blood cultures and the course of the disease. Differentiation from *pyemia* without endocarditis must be made on changes in the heart signs, the evidences of recurrent embolism and the clinical course of the disease, and this applies also to the differentiation of *concealed foci of suppuration* in which cases a positive blood culture is also of great value. The differentiation from the *blood diseases* is based on the fact that the blood picture is, in many cases, not characteristic and that the cardiac changes and evidences of embolism are not part of the clinical picture of the anemias. *Inflammatory abdominal conditions* are differentiated by the history of the case, the cardiac signs and the evidences of embolism in various parts of the body.

PROGNOSIS

The general statement regarding prognosis in subacute bacterial endocarditis is that recovery is exceedingly rare. Billings states that out of more than 100 patients with this disease he saw 3 recover, and 1 had no heart murmur. Libman in 1920 stated that he had seen 4 complete recoveries in over 150 patients. Other observers have noted isolated instances of the disease with recovery (Hemsted, Jochmann, Schottmüller, Lorey, etc.). The writer had under observation one patient, a young man with a chronic rheumatic mitral and aortic endocarditis, who ran a septic fever for fifty days and then recovered

completely. Streptococcus viridans was isolated from the blood on the seventeenth day of fever. From the large series of cases of Libman and Frank Billings we may conclude that recovery occurs in from 2 to 3 per cent of patients who appear to be suffering from subacute bacterial endocarditis. It is necessary to point out, however, that where no heart murmur is present or where there is an old heart lesion without modification of the signs it is impossible to prove that fresh endocarditis is present, and recovery from streptococcus viridans sepsis without endocarditis is by no means unknown.

There are two groups of patients reported in the literature as subjects of endocarditis due to streptococcus viridans in whom there was practically no mortality. In 1915 Oille, Graham and Detweiller published a series of 23 cases, mostly young women with symptoms suggesting neurasthenia, anemia, tuberculosis or gastric ulcer, from whose blood streptococcus viridans was isolated. The patients had heart murmurs, usually in the pulmonic area but interpreted as of mitral origin and generally unaccompanied by enlargement of the heart. Many of the patients had no fever, and none of them showed petechiae though one of the series showed painful subcutaneous nodules on the hands. In 1920, in an article dealing mainly with the bacteriology of streptococcus viridans, Salus reports 18 cases from Funke's clinic which he describes as endocarditis lenta. He states that they were characterized by mildness of symptoms, low temperature, frequency of leucopenia and relative benignity. The great majority of the patients were still able to work at the end of twelve to eighteen months.

Salus' paper gives no clinical details regarding Funke's patients and we do not know upon what grounds the diagnosis of endocarditis was based. In the group of patients reported by Oille and his associates it is to be noted that the murmurs were most frequently in the pulmonic area (the area of auscultatory romance), that many of the patients had no fever, and that hardly one of them had any lesion suggesting embolism. While it is conceivable that a group of patients living in the same locality might become infected with an extraordinarily subvirulent organism we submit that one may legitimately be sceptical as to the correctness of the diagnosis of endocarditis in both of these series. They are, however, of decided interest and in view of the pathological work of Reye should certainly not be discarded as entirely unworthy of credence.

PROPHYLAXIS

The intelligent prevention of subacute endocarditis demands consideration of the various factors concerned in its production. As Horder had pointed out these factors are:

1. The primary focus
2. Lowered tissue resistance
2. A damaged endocardium
4. The infective agent

In the section on etiology we have pointed out that the primary focus is often unknown because the insidious character of the disease permits of healing before a search is made. It is nevertheless fairly certain that local foci of infection in the teeth, tonsils, sinuses, female genitalia, and other parts of the body of which streptococcus viridans may be a normal inhabitant, are not infrequently associated with subacute bacterial endocarditis. It is further known that in some instances the same organism may be isolated from the local focus and the blood stream. It seems only logical, therefore, to insist on the importance of the removal of such local foci, particularly in those individuals who give a history of rheumatism with or without endocarditis.

It is questionable whether in the present state of our knowledge it is possible to separate lowered tissue resistance in a general sense from the effects of cardiac damage. In the case of a rheumatic patient without apparent heart damage we do not known whether there is some general lowering of the resistance to Streptococcus viridans or whether there is clinically undiscoverable heart damage which is responsible for undue local susceptibility. We do know that rheumatism is frequently preceded by tonsilitis and at times by other focal infections so that the whole question of the desirability of eradicating infectious foci comes into question. No one, we believe, would doubt the wisdom of dental prophylaxis, or of the eradication of chronic sinus or ear disease. The focus concerning whose removal there does seem to be some difference of opinion is the tonsil. Krehl has shown that *drainage* of infected tonsils does not suffice to prevent rheumatism and it would seem logical therefore in the absence of obvious contraindications to remove these organs when infected. Until the etiology of rheumatism is finally

cleared up we shall not, of course, have an entirely clear conception of the procedures necessary to prevent this disease but that is no reason why the application of such methods as now seem logical should not be carried out.

The question of the *infective agent* is so closely bound up with that of the foci in which it is found that at present little can be said regarding removal of the organism by methods other than elimination of such foci. Theoretically it might be possible by the preventive inoculation of rheumatics and cardiacs to produce an immunity to streptococcus viridans or bacillus influenzae. Theoretically also bacterial substitution therapy or chemotherapy might in the future be developed to a degree permitting of the elimination of these organisms from the body. We have not found any references in the literature which indicate that any serious attempt to utilize such measures has been made.

TREATMENT

A patient with subacute bacterial endocarditis requires the ordinary *hygienic and dietetic* treatment of a febrile case. Rest in bed, plenty of fresh air, free water drinking unless some contraindication exists, and a soft, easy digestible diet are all essential. In some of the more chronic cases heliotherapy may be of benefit. The bowels and skin should receive careful attention. Obvious local foci of infection should be eliminated if this can be done without too great shock to the patient. Some authors recommend quinine as a general tonic; Horder gives it in doses of 5 grains every four hours. It goes without saying also that symptoms must often be treated as they arise. Cough, pain, gastro-intestinal upsets, hyperpyrexia or other unpleasant features demand the usual treatment. The painful joints may be relieved by local applications and salicylates though Schürer says the coal tar products, such as antipyrin or melubrin give more relief.

The literature contains many references to *vaccine treatment* in this disease, and in general, it is stated that such treatment is of little or no value. Some writers, Babcock, Fette and Gilman Thompson for example, think that the course of the disease may be influenced to some extent by vaccine therapy; others, Debré and Scheidemantel for example, think it is useless. Osler thinks it has proved its value in a few cases. Emerson and Harrison report a recovery under vaccines.

Frank Billings states that in modified pneumococcus cases vaccines are not only useless but harmful. *Autogenous vaccines* administered subcutaneously or intravenously have been used in almost all the reported cases in doses of from 2,000,000 to 50,000,000, and at intervals ranging from daily to every five days. Latham and Hunt recommend autogenous vaccines by mouth. They give doses of from 2,500,000 to 30,000,000 bacteria in 10 cc. of normal salt solution on an empty stomach one hour before food. They report the recovery of one patient after an illness of fourteen and a half months. A careful scrutiny of the records of those patients in whom benefit has been claimed leads to the suspicion that either the natural course of the disease or perhaps a non-specific effect like protein shock has led to a temporary amelioration of symptoms.

Sero-therapy either in the form of stock antistreptococcic sera (Tavel, Höchst) or of specially prepared sera made by inoculating animals with the organism isolated from the patient's blood, has been tried in many patients, usually with unsatisfactory results. E. G. Janeway states that he has seen no benefit from serum treatment. Debré says that polyvalent serum has no effect. Horder states that autogenous serum is ineffectual. Steinert has used Tavel's serum without result. On the other hand Steinert states that he saw slight temporary effect in one patient from autogenous serum and Debré had a similar experience.

Hemsted, Horder and Jochmann, think that a *combination of autogenous vaccine and serum* prepared from the patient's own infecting organism offers the best hope for recovery. Hemsted's patient recovered after eleven months of treatment, four months of autogenous vaccines in doses of 2,000,000 to 15,000,000, followed by five doses of serum and again by vaccines. The serum was discontinued after five doses on account of anaphylactic phenomena and one may speculate whether the anaphylactic shock may not have been a factor in helping to bring about cure.

Autoserotherapy was successfully used by Abrahams in one patient with streptococcus viridans septicemia. Twenty cubic centimeters of the patient's own serum were injected intravenously on three successive days. After the third injection the organisms disappeared from the blood. It is not clear, however, that an endocarditis was present in this patient although there was a heart murmur.

Transfusion of blood has occasionally been resorted to. Lamb's patient received 2500 cc. of blood in eleven transfusions and Lamb believes that life was prolonged. Kinsella states that transfusion may cause a decrease in the streptococci in the blood if it produces a febrile reaction. Lamb states that transfusions with blood from *a vaccinated donor* is useless and one personal experience with this method supports this view.

No record can be found in the literature of any attempt to stimulate the opsonins by the injection of *nuclein* though the work of Fox and Lynch suggests that this method is at least worthy of a trial.

Various *chemical substances* have been employed in the treatment of subacute bacterial endocarditis. Various preparations of *silver* (colloidal silver, collargol, dispargin, electrargol, argochrom, ungentum Crédé) have been used by various methods but all without definite effects. Leschke has tried *optochin* and *isoamylhydrocuprein* in massive doses without influencing the disease. *Quinine, hexamethylenamine, mercury and salicylates* have all been employed in vain. Debré states that *arsenic* is valueless though Lorey reports one apparent cure from *salvarsan*. Frank Billings on the contrary is convinced that when an early diagnosis can be made *sodium cacodylate* is of decided value. He uses from 10 to 15 grains of the drug hypodermically every two or three days for a month and then resumes treatment after an intermission of a week. From 10 to 15 grains may be given intravenously every two or three days for two weeks and may be resumed after an intermission of a week. Boyd tried *Eusol*, 60 cc. intravenously, but the patient developed pain in the chest and became unconscious and the treatment was not continued.

A critical survey of the results of treatment cannot fail to leave one in a pessimistic frame of mind regarding any form of therapy so far developed. The patients who have recovered are few, probably not so numerous as those who have recovered spontaneously without treatment, and the beneficial effects produced in patients who ultimately died are possibly due to spontaneous remissions or other factors than a specific action on the causal agent of the disease. It is difficult to estimate whether the greater hope for future therapy is along the line of immunotherapy or chemotherapy. There would seem to be possibilities in either direction.

PROBLEMS OF THE FUTURE

The unsolved problems connected with subacute bacterial endocarditis have already been discussed to some extent in the different sections. It seemed wise, however, to bring them together into one place at the end of the review.

1. *What is the relationship between subacute bacterial endocarditis and acute articular rheumatism?* Inasmuch as the rheumatic factor is the preponderating one in the production of subacute bacterial endocarditis this is the most important unsolved problem. The answer to this question involves several other questions, viz.: the etiology of rheumatism; the relationship of streptococci to rheumatic endocarditis: whether rheumatism per se is the factor predisposing to endocarditis or whether the rheumatic cardiac changes are the important elements.

2. *How is a subvirulent streptococcus able to cause a grave general infection?* Do these organisms gain enhanced virulence in local foci of infection? Are the protective body reactions at fault in individuals who contract subacute bacterial endocarditis and if so in what detail? Are the local powers of resistence in the damaged heart lessened by a previous endocarditis or are there circulatory changes in the damaged valves which favor reinfection? Is sepsis lenta the sepsis of highly resistant individuals as Kuczynski and Wolff believe as a result of animal experiments? Does the streptococcus viridans immunize itself against the antibodies of its host?

3. *What is the relationship of subacute bacterial endocarditis to other forms of bacterial endocarditis?* This question really involves the answers to questions 1 and 2, as it concerns rheumatism and the immunological conditions of the disease.

It can be seen from these questions that there are many problems yet to be solved in connection with this disease and that they are problems which have a much wider bearing than the etiology of endocarditis. The whole question of infection with subvirulent organisms is concerned and also the solution of the etiology of the rheumatic group of infections. Incidentally the question of the classification of streptococci and their relationship to pneumococci is involved.

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EDEMA

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I. INTRODUCTION

Edema is a pathological condition in which fluid accumulates excessively in tissues or cavities of the body. It is due to an interference with the mechanism which regulates the water content of the body fluids and tissues, and which tends to keep it constant within certain limits and to correlate it with the salt content in such a way that the osmotic pressure likewise remains approximately constant. A series of processes participates in the maintenance of the water and salt level and it appears probable that these processes are, to a certain extent, correlated with each other in such a way that one regulatory mechanism results, comparable to the mechanism which regulates the constancy of the hydrogen ion concentration in the body fluids.

Water and salt are taken in essentially through the gastro-intestinal canal; both are absorbed and enter the blood. Through the heart action, aided by vasomotor mechanisms, the water and salts are distributed by way of the capillaries among the various tissues. Some of the fluid leaves the blood through the capillaries and thus reaches the constituents of the tissues proper. Metabolic products of the tissues are mixed with this blood transudate. Both combined constitute the interstitial fluid. A part of this is reabsorbed through the blood-vessels, another part enters, through the endothelium of the lymph vessels, into the lymphatic system and thus becomes lymph, which ultimately is again carried to the blood stream. Related to the interstitial fluid is the fluid which is found in the serous cavities, although this is apparently modified through the influence of the membrane lining these cavities.

The constant intake of water is compensated for by a continuous elimination of water through the kidney, skin and lung. We know that the intensity of elimination is regulated by the intensity of water drinking, and that the intensity of water drinking depends, to a certain extent, upon the intensity of water elimination. We know furthermore that there exists between the various mechanisms which take care of the water elimination, a correlation of such a nature that diminished activity of one organ is compensated for by an excess activity of another organ.

There is in addition some evidence which suggests that further regulating mechanisms exist, which provide for the elimination of

fluid through the capillary walls. These act in such a way that interference with the function of the heart or kidney or a localized disturbance in certain tissues, which would tend to change the amount and composition of the circulating body fluids, leads to an increased transudation of fluid from the blood capillaries into the tissues and into the serous cavities. In certain respects such an increased transudation may be considered as a safety process tending to maintain the condition of the blood constant. But if this last mechanism is more than a transitory expedient, which is at once compensated for by increased absorption, it becomes pathological in itself and represents edema.

The water contained in the circulating body fluids as well as in the interstitial tissue and in the tissues proper enters into relations with salts and colloids, particularly proteins, and both of these substances thus become factors which help to determine the quantity of water which is held in various parts of the body, and which influence the passage of fluid through the membranes separating the blood and lymph channels from interstitial tissue, serous cavities and organ tissues proper. In addition, evidence has been found in recent years which shows that various organic substances, among which are certain hormones, may influence likewise the direction of the movement of the body fluids and may thus become a factor in the abnormal accumulation in, and in the discharge of fluid from the body.

We see then that the factors underlying edema are not identical with those determining the formation of lymph, although both have some factors in common, namely, transudation and tissue activity; but elimination through the lymph channels may play a certain part in compensating for an increased transudation, and obstruction of the lymph channels in certain cases may lead to a back current of fluid into the interstital tissue. However, the production of edema depends on conditions which are not necessarily directly concerned in lymph formation and an analysis of edema is therefore not identical with an analysis of lymph formation.

Interference with any of the factors which participate in the regulation of the mechanisms which tend to maintain what might be called homoiohydria and homoiotonicity may lead to edema. Deficiencies in the movement and distribution of blood, in the elimination of fluid through the kidney and in the transudation and absorption process

through capillaries and lymph vessels may lead to edema, but these various factors are of unequal importance in so far as faulty movement of blood and faulty elimination of fluid affect the transudation process, and act therefore essentially through an interference in the exchange of fluid between the capillaries and tissues.

As in other functions of the living organism, we have in some of these mechanisms, which regulate the distribution of fluid in the body, to deal with chain reactions in which an initial change or stimulus leads to a series of subsequent changes. Some of the elements constituting the different chains may be identical and the same elements of a chain may thus recur in several series.

A perfect analysis of edema would presuppose a complete knowledge of the various chains and especially of those elements of chains which are found in several or all of the series. These elements we would consider as the real causes of edema. However, at present our knowledge of the various chains is still incomplete, although we know some of the important elements of the chains which recur in several series, and in particular are we unable at present to state in most cases the sequence in which the different elements are joined to each other.

This consideration is of some importance in the classification of the various kinds of edema. We might use for the purpose of classification the initial factors in the various chains, or, on the other hand, we might try to sift out the important elements in the reaction chains which follow the initial interference.

As we stated, these elements are insufficiently known; the relative importance and sequence of various elements are uncertain; furthermore, similar elements recur in different series. A classification based on these elements would therefore be uncertain. We shall discuss the various chains separately and use for classification the initial elements of the chains. In each case the essential object of investigation concerns the character of the succeeding elements and the order in which they follow each other.[1]

[1] We shall consider in more detail the publications of approximately the last fifteen years and make only brief references to the older literature. More complete references to the latter are found in Meltzer, Lectures on Edema, American Medicine, 1904, Vol. 8, p. 19 and subsequent numbers. R. Magnus, Bildung d. Lymphe., Handbuch d. Biochemie Vol. 2, II, p. 99. H. Gerhartz, ibid., p. 137. R. Klemensiewicz d. Pathologie d. Lymphstroemung. Handbuch d. allgem. Pathologie (Marchand u. Krehl), Vol. 2., I Ab., p. 341. See also a presentation of edema by H. G. Wells, Chemical Pathology, III Edition, p. 339, and M. H. Fischer, Edema and Nephritis, New York, 1915.

II. CHANGES IN THE PERMEABILITY OF BLOOD-VESSELS IN LOCALIZED EDEMA

A. Varieties of local edema

Some of the most important recent contributions to the study of edema concern an analysis of the factors that influence the permeability of blood-vessels, and the significance of these factors in the origin of edema. However, the conception of a change in vascular permeability as a cause of edema is rather old and the first observations reach back a considerable number of years. In order to appreciate the significance of these factors, it is necessary to give a brief résumé of the more important investigations gradually leading to the recognition of a variable permeability of the capillaries as a factor in the origin of edema.

Grainger Stewart and Bartels had expressed the opinion that renal edema was caused by a retention of water, the result of renal deficiency. The experiments of Cohnheim and Lichtheim did not altogether substantiate this view. The later investigators showed that small amounts of sodium chloride solutions could be injected intravenously into rabbits without edema developing subsequently. However, when very large amounts were infused, ascites and edema of the gastrointestinal canal, around certain glands, and in restricted parts of the interstitial tissue elsewhere, resulted; but the thoracic cavity and particularly the subcutaneous tissue remained essentially free from edema. When, however, local irritants (iodine, heat) were applied to the skin, the experimental hydremic plethora was followed by an edema in the affected area. Likewise, ligating the femoral vein, which in itself did not lead to edema, caused edema in hydremic animals. Similarly a temporary complete interruption of the circulation in a certain area may lead to edema of this area after the reestablishment of the circulation. Several conclusions may be drawn from these experiments: (1) A hydremic condition of the blood does not necessarily lead to edema. (2) It may lead to edema in parts of the body, when combined with an increased permeability of the vessels, where hydremia alone did not have this effect. (3) Hydremia in conjunction with passive congestion also may lead to edema. (4) Increased permeability of the vessels alone may give origin to edema.

These conclusions were confirmed and extended by Magnus who showed that intravenous perfusion of dead rabbits with a solution of sodium chloride led to general edema (including anasarca). In the living animal poisoning with arsenic and other substances, which were supposed to affect the blood-vessels, as well as a preceding occlusion of the ureters had similar consequences in the perfused rabbits.

However the significance of an increase in the permeability of vessels as the cause of edema can be shown more directly through the study of localized edema. These edemas furthermore lend themselves more readily to an analysis of the action of substances influencing the permeability of the capillary blood-vessels and thus modifying the course and intensity of edema.

To this category of localized edema belongs in the first place the edema accompanying inflammation. Related to the ordinary inflammatory edema are localized edemas which occur in conditions, which are either anaphylatic in character or at least closely resemble anaphylatic phenomena. The reaction against tuberculin in individuals infected with tubercle bacilli, or injected with certain of their products, the positive Schick and Luetin tests, are of such a character. Whether these reactions are truly anaphylatic or merely resemble anaphylatic reactions is a matter of dispute at the present time.

Edematous conditions resembling the exudative diathesis of Czerny which occurs in childhood may in some cases be due to anaphylaxis (Schultz and Larson). In sensitized individuals in whom a second injection of the antigen has been given, a non-specific irritation of the skin may cause a very pronounced edema, which Auer interprets as due to the accumulation of antigen in the lymph at the place of irritation. In urticaria or in related conditions, such as are caused through the ingestion of certain substances in predisposed individuals or through intradermal injection of certain substances like histamin (Eppinger), morphine, atropin, formaldehyde, concentrated calcium chloride (Philippson, Th. Sollmann and Pilcher), we have to deal with a localized edema, probably due to alteration of capillaries (Gilchrist, Jadassohn and Rothe). There is not only transudate present in these cases, but even some emigration of leucocytes and edematous swelling of cells and connective tissue fibers. Certain substances like arsenic, chloral, salicylates and others, which produce clinically

urticaria, do not have this effect after intradermal injections. Local acidosis can be excluded as the cause of these edemas (Sollmann and Pilcher).

Related to this class of edemas is the toxic edema which is produced through bacterial toxins or through the action of light in individuals, in which a photosensitizing fluorescent substance is circulating in a quantity sufficient to cause an injurious effect of light rays. Thus Hausmann could produce extensive edema of the skin in mice injected with haematoporphyrin and subsequently exposed to light. If the Laewen-Trendelenburg blood-vessel preparation is perfused with fluid which contains fluorescent substances, edema is produced in the perfused legs (Adler). In these cases the vessels are probably injured through the circulating fluid. Certain exudative skin affections are perhaps due to the combined action of a sensitizing substance and light.

A similar injury to the endothelial cells of the capillaries may, according to Findlay, explain the edema which is found around the capillaries in the scurvy of guinea pigs. Deficient nourishment produces an injury to the wall of the capillaries, which at first allows only the escape of plasma from the blood-vessels; and only if the injury becomes more marked an escape of erythrocytes follows. We may assume that the permeability of the capillaries is thereby sufficiently increased to cause edema.

Somewhat related to this toxic effect on the endothelia of blood-vessels in the Laewen-Trendelenburg preparation is the edema produced in this preparation, if, according to Zwaardemaker and Ginzburg, Locke solution which has been deprived of its potassium content, is used as a perfusing fluid. These authors attribute this result to the lack of the beta rays given off by the radioactive potassium and they are able to substitute for potassium certain other radioactive substances in definite proportions and thus prevent edema. These experiments likewise point towards the reaction of the endothelium as an important factor in edema. Of interest is also the observation of these authors, that uranium or other heavy radioactive substances, while beneficial if acting as substitutes for potassium or rubidium, may antagonize the effect of potassium if used in combination with this substance. This effect may possibly have to be considered in explaining the very marked edema producing power of uranium salts.

These observations are however interpreted differently by R. T. Hamburger, who finds that the relation of Ca, Na, and K ions in the perfusing fluid is the determining factor. A certain concentration of Ca ions tends to make the capillaries impermeable and at the same time causes a constriction of the vessels, while potassium ions, if not counteracted by calcium, tend to have the opposite effect. Hamburger finds that a mixture of Na and Ca ions is able to prevent edema, provided Ca ions are present in sufficient quantity. Potassium ions are not necessary for this purpose.

We shall again refer to the significance of the capillary wall in the production of edema and particularly to the analysis of variable factors concerned in this process in the next chapter, where we shall discuss still further the factors which affect the permeability of blood-vessels.

Under certain conditions the application of alkali increases the permeability of the skin. Thus Jacoby has shown that alkali and veronal, as well as saponin, make it possible for very small amounts of adrenalin, which alone would be ineffective, to penetrate the frog-skin and to affect the vessels. This author suggests that carbon dioxide may increase the permeability of the capillaries indirectly by making available OH ions, which would combine with lipoids or proteins of the cells and thus influence the permeability of the latter.

Various authors attribute also edema of renal origin to a generalized change in the blood-vessels. They assume that uranium nitrate produces changes in the permeability of the blood-vessels. Functional alterations in the vessels following the administration of this substance we shall discuss later in connection wtih renal edema. Fleckseder found in addition structural changes in the renal vessels and peritoneal ecchymoses after administration of uranium, but these findings hardly permit the conclusion that uranium salts cause structual changes in the blood-vessels generally.

In this connection we may also discuss the so-called angioneurotic edema. It is a localized edema which is particularly prone to appear in the skin, but may also appear in mucous membranes or in the brain. H. Quincke, who designated it "angio-neurotic edema," assumed formerly that it was caused by a localized and transitory change in vasomotor function. Two kinds of data seem to support such a conclu-

sion: (1) It has been observed that it may occur under the influence of emotions and in hemicrania. Its unilateral localization might suggest a more peripheral point of attack of the nervous mechanism. (2) Certain experimental facts indicate that hyperemia, caused through paralysis of a sufficient number of vasomotor nerves, may call forth an increased transudation of fluid from the blood-vessels into the tissues and temporarily an increased lymph flow in this area. In these cases however the transudate does not usually accumulate in the tissues and edema does not ensue. Active hyperemia also may lead to increased transudation and even to edema. The latter has been produced through electric stimulation of the peripheral end of the lingual nerve in dogs. If the hyperemia is sufficiently strong and long continued, edema of half of the tongue may follow. While we must thus concede the possibility that vasomotor nerve changes may lead to localized edema, it is by no means certain that this is the mechanism which actually is implicated in the so-called angio-neurotic edema. Indeed H. Quincke himself has recently abandoned this interpretation and holds changes in the tissues, which lead to an increased attraction of water, primarily responsible. But this too is merely a hypothetical assumption.

In analogy to other strictly localized edemas it appears most probable that changes in the permeability of blood-vessels in circumscribed areas, due to the action of toxins, are the direct cause of this kind of edema. Some cases of the so called angioneurotic edema seem to be due to a hypersensitiveness to certain proteins, especially those contained in food. They would thus represent types of localized, exaggerated urticaria (observations of Walker, Phillips and others).

In certain cases the tendency to this edema seems to be inherited. Cases of inheritance have been observed by various authors and recently a similar observation has been reported by the Crowders.

B. Functional and toxic changes in the permeability of blood-vessels. Inflammatory edema

Recent observations tend to prove that dilatation of the capillaries increases the permeability of the vessel wall and is followed by a movement of blood plasma from the interior of the vessel to the

surrounding tissue. Sherrington and Copeman found that various operative procedures, especially those tending to produce shock, caused an increased specific gravity of the blood, and they interpreted this as due to a movement of the blood plasma from the vessels into the tissues. According to Heubner a series of substances act as capillary poisons, diminishing the tone of the endothelial cells, leading to a dilatation of the capillaries, to stagnation of the blood and to a lowering of blood pressure, thus bringing about a condition comparable to internal bleeding. But these substances may also cause true hemorrhages by diapedesis, as the result of a loosening of the cement substance between the endothelial cells. Emetin, sepsin, salts of heavy metals (gold, sodium salts) may act in this way. More recently Dale, Laidlaw, Richards and Rich have shown that histamin causes on the one hand a dilatation of the capillaries and a movement of the plasma from the blood vessels to the tissues, and on the other hand a contraction of the smooth muscle layer in arterioles and bronchi. Application of this substance thus imitates the conditions found in shock. The studies, particularly of Krogh, Hooker and others, have made certain the general conclusion that capillaries can contract and dilate independently of changes in the arterial wall. Chemical as well as mechanical stimuli may have such an effect, producing especially vasodilatation. Few substances lead to constriction. Adrenalin in larger doses seems to act thus, while in smaller doses it may lead to a dilatation.

A direct demonstration of the escape of plasma through pores in the capillaries, after chemical stimulation through urethan, has recently been given by Krogh and Harrop. Soluble starch and colloidal dyes leave the blood vessels under those conditions, while particles of India ink are held back. An increase in intracapillary blood pressure is not responsible for this increased permeability.

According to Hooker chemical stimulation leads to a dilatation of capillaries and increased transudation, while nerve stimulation counteracts these influences. Krogh has furthermore shown that every normal muscular activity leads to a dilatation of the capillaries. An increase in permeability occurs in response to tissue needs, if carbon dioxide and other metabolic products accumulate (Krogh). Hess and Fleisch have shown generally that a physiological increase

in hydrogen ion concentration in actively metabolizing tissue may lead to a dilatation of the blood-vessels.

This dilating effect of stimuli explains the condition in inflammation, particularly the production of inflammatory edema. If the dilatation caused by abnormal stimuli is sufficiently marked, plasma leaves the vessels, the viscosity of the blood increases (Trevan) and stasis may result.

Quite recently Krogh and Rehberg have made it very probable that pituitrin maintains the tonus of the capillaries. Ringer's solution alone, serving as a perfusion fluid for the blood-vessels of the frog, causes a dilatation of the capillaries and *pari passu* an escape of the fluid from the vessels into the interstitial tissues. Addition of pituitrin in very low concentration prevents this process by maintaining the tonus of the capillaries. There is reason for assuming that the substance present in the normal serum, which has a similar effect on the vessels, is identical with pituitrin.

In this connection we must again refer to the influence of ions on the permeability of the blood-vessels. Gunzburg found that if the frog preparations are perfused with Ringer's solution, edema does not follow, but if potassium is omitted from the solution the legs become edematous. Subsequently R. J. Hamburger has shown that the permeability of the capillaries depends on the quantitative relation between Na, K and Ca ions in the perfusing solution; in the same way as in some other cases Ca counteracts also in this case the Na and K ions. A fluid consisting of Na and Ca ions used in correct proportions prevents edema, even if potassium is absent. Addition of too much potassium on the other hand caused edema. Calcium causes a tightening of the vessel wall and if added in still larger quantity to the sodium chloride solution, it may produce an extreme contraction of the vessels. It may be assumed that the tightening of the vessel wall, resulting in lessened permeability, and the process of constriction of the vessels are related and associated processes. As we have shown previously the contrary condition also holds good, a dilatation of the capillaries may be accompanied by a greater permeability of the vessel wall. In a similar way an increase of the oxygen tension of the perfusion fluid tightens the vessels, prevents edema and may cause contraction of the vessel wall.

There is also some direct evidence pointing to changes in the permeability of blood-vessels in the origin of experimental or clinical edema. Quite recently Morawitz and Deneke have devised a method which enables them to recognize functional changes in the permeability of the blood-vessels. They determine a change in the concentration of the blood following a compression of the vessels of the upper extremity. An abnormal reaction indicating an increase in permeability was observed in acute and chronic glomerulonephritis, but also in certain other diseases even if they are not accompanied by edema, as for instance, typhoid, scarlet fever, purpura, endocarditis and carbonmonoxide poisoning. In these latter diseases there is indeed some reason for assuming the presence of vascular lesions; on the other hand in a case of cardiac edema and in edema due to undernourishment, normal vascular reactions were found. We would then have to assume that in the latter kinds of edema vascular injuries are not a prominent factor in the causation of edema, in contradistinction to kidney lesions where they are of etiological significance. While in experimental conditions leading to edema, particularly in uranium nitrate poisoning, changes in the permeability of blood-vessels have been found also by other means, they are the opposite of what might have been expected. Thus Boycott and Chisholm and others found a slowing of the rate of elimination of certain substances from the blood-vessels in the later stages of uranium poisoning, a condition in which edema is a prominent feature. We shall have occasion to refer to these experiments again in a subsequent chapter.

While, thus, recent investigations clearly demonstrate the importance of changes in the permeability of membranes in the origin of inflammatory and toxic edema, there has also been forthcoming some new evidence which tends to show that there must be added to the increase in permeability filtration pressure, if edema is to result. Thus Hirschfelder has shown that the inflammation, which in the rabbit follows instillation of mustard oil in the conjunctival sac, requires a certain intensity of blood pressure. In animals, in which through measures of a mechanical or toxic character, the blood pressure has been lowered to a certain level, edema does not develop. Even injection of peptone, which as a lymphagogue of the first order is supposed to increase the permeability of membranes and thus

increase edema, may prevent edema, if it causes a fall in blood pressure below a certain level.

We may then conclude that functional as well as toxic influences cause frequent variations in the permeability of the blood-vessels. It may be assumed that there is a graded increase in permeability from that produced by purely functional conditions to that caused by toxic and inflammatory stimuli in general, which latter permit even cellular motile elements to pass through the wall of the vessels. The greater the permeability, the greater the amount of molecules of large size and particularly of colloids, which can pass through the vessel wall.

Even with normal capillaries, a certain amount of colloid passes out of the blood-vessels together with water and salts. A reverse current also occurs. While in certain cases protein-free fluid can perhaps enter the blood-vessels, usually some protein is mixed with this fluid. This for instance can be shown to be the case if a relatively large quantity of water is administered to a rabbit. At different periods water moves in this case in or out of the blood-vessels, together with some protein (Oehme). The character of the diet given previously determines to some extent the direction in which the fluid moves. Nonnenbruch likewise observed that protein may move with the water into the blood-vessels. This fact makes it clear that refraction determinations cannot serve as a satisfactory indicator of changes in the blood volume.

In some respects the vessel wall may be compared to a membrane, the properties of which are variable, but which in general retains more readily large molecules than smaller ones and through which, for instance, solutions of glucose are held back to a greater extent than sodium chloride solutions. It may behave on the one hand like the filters devised by Bechhold for ultrafiltration, or it may resemble a filter with relatively coarse pores; there are all kinds of graduations between these two extremes. In general we may state that factors which tend to cause a dilatation of the vessels and to decrease the tonus of the capillaries, tend to increase the permeability of the vessel wall and thus to favor the production of edema, and that contraction of the vessels has the opposite effect. These variations in permeability of the vessels are an important factor in the origin of edema.

C. Shock and edema

While shock, experimental or clinical, is not known as a cause of edema, still the intensive study of shock made during the recent war is not without interest for the analysis of certain factors that underlie edema. Cannon designated as exemia, a condition preceding and responsible for shock; it is an overfilling of capillaries with blood in certain areas of the body and a transudation of plasma from the vessels into the tissues. These two factors cause a diminution in the efficient blood volume. Dale, Laidlaw and Richards have shown this condition to be very pronounced in shock produced by injection of histamin. Erlanger, Gasser and Gesell analysed the circulatory factors in a variety of conditions associated with shock and found, common to all of them, an engorgement of the splanchnic capillaries and vessels with blood and a considerable transudation of plasma, as the result of a localized slowing of the circulation combined with a dilatation of the capillaries; in addition there may be an increase in capillary pressure in certain cases. Of special interest is the observation of these authors that if shock follows injection of adrenalin, each successive injection of adrenalin produces a concentration of blood greater than the preceding one. Each injection must therefore have left a residuum of damage which became so intense after the third injection that the plasma did not return to the vessels as before; in the non-injured body, on the other hand, according to the interpretation of Starling, the plasma is supposed to return to the vessels in places, where the blood pressure is lower. Thus we have brought about a condition which, if continued over a sufficient period of time, would lead to edema.

To counteract this diminution in the effective blood volume in shock, Bayliss used an isotonic solution of the colloid gum acacia, while Erlanger and Gasser employed hypertonic solutions of this substance in combination with a hypertonic solution of glucose. They find that the acacia injected intravenously attracts water very slowly into the circulation as compared with the crystalloid glucose. It does not hold the water in as large a quantity as would be expected on the basis of its osmotic pressure and the maximum blood volume reached is not maintained, although the blood volume is held at a higher level longer than after injection of hypertonic solution of glucose.

F. E. Meyer and Seyderhelm find a Bayliss solution effective in counteracting the influence of a loss of blood on the size of the heart, in contradistinction to Ringer's solution which is not effective in this respect. On the other hand, according to Nonnenbruch, after intravenous injection of a Bayliss solution in rabbits, the blood volume returns to the normal condition as early as two to three hours following the injection; in this respect it acts not differently from Ringer's solution. The injection of hypertonic acacia solution, on the other hand, this author finds more effective.

The hypertonic acacia-sugar solution thus prevents, during the period of acute shock, an excess of plasma from leaving the circulation, provided the damage to the vessel wall has not caused a very considerable increase in the permeability of the blood-vessels.

We see then in shock the same increase in transudation of plasma which is characteristic of edema; but in shock we have to deal with an acute condition, in which a considerable part of the fluid returns to the vessels, and in which the process of transudation, lasting only during a relatively short period of time, is not sufficiently extensive to become manifest as edema. At the same time we have found indications that the beginning of edema may be produced experimentally in these conditions, provided a gradation in intensity of the shock is accomplished.

D. The rôle of sensory nerves in inflammatory edema

G. Spiess drew attention to the fact that local anesthesia prevents or diminishes the edema which is due to the action of toxic substances. He attributed this effect to the elimination of pain, which latter was supposed to cause a reflex dilatation of the blood-vessels. Thus inflammatory edema may be lacking in anesthetic areas, even in those found in cases of hysteria.

In accordance with this conclusion Januschke found that the edema following the application of mustard oil can be prevented not only by the use of calcium salts, but also by adrenalin and various anesthetizing substances, like ether, morphine, chloralhydrate and also by antipyrin, quinine and sodium salicylate. According to Starkenstein and Wiechowski injection of atophan has a similar effect; this latter observation was however not confirmed by Heubner.

The effect of anesthetics upon inflammatory edema suggested the participation of reflex mechanisms in this process. The mechanism of dilatation of vessels in inflammation which is followed by transudation has been analysed by A. N. Bruce, who concludes that it is due to an axon reflex. The application of alypin prevents this inflammatory reflex. Brady, on the other hand, interprets this reflex as due to the stimulation of sensory nerves which inhibits the constricting action of sympathetic ganglia, and thus leads to an inflammatory dilatation of the vessels. Anesthesia, in eliminating this inhibiting effect of sensory nerves, maintains the constricting action of the sympathetic ganglia.

However more recent experiments do not entirely confirm these conclusions. According to Breslauer a local reflex, which may be inhibited through local anesthesia of the affected skin or mucous membrane, is responsible only for the primary active inflammatory hyperemia; the later phases of inflammation on the other hand are not influenced by local anesthesia. Elimination of pain sensation is not concerned in this process. Different again are the conclusions of Groll, who finds that anesthesia, or even degeneration of the nerves leading to a certain area, is not capable of preventing the primary inflammatory hyperemia which he considers as paralytic. However, cocain as well as various other anesthetic substances, can diminish the chemosis following the application of mustard oil to the conjunctiva. The effect of these substances cannot be due entirely to vasoconstriction, because atropin and veronal which dilate the vessels have a similar influence. He concludes that substances producing inflammation act directly on the neuromuscular apparatus of the blood-vessels.

It is probable that the effect of anesthetics and some other substances in diminishing certain phases of the inflammatory reactions and particulary inflammatory edema, is due mainly to their direct action on the neuromuscular apparatus of the blood-vessels, but in addition they may perhaps also cause a vasoconstriction by reflex mechanisms. However that may be, for us it is important to know that various substances are able to diminish the transudation from the blood-vessels through their effect on the permeability of the blood-vessels. In certain cases this diminution in the permeability of the blood vessels

is apparently associated with a constricting effect on the blood-vessel wall (adrenalin); in other cases these substances prevent directly or reflexly a dilatation of the capillaries and an increased permeability.

Above we have referred to the experiments of Hirschfelder which have shown that, in addition to the factors named, a certain intensity of blood pressure is a necessary condition for the development of this inflammatory edema. A lowering of the blood pressure below a certain point may prevent it because it is the filtration pressure which drives the fluid across the vessel wall into the surrounding connective tissue. However, under normal conditions the filtration pressure required for transudation is always present; the variable factor is therefore the change in the permeability of blood-vessels; this is altered in inflammation and to a less degree it varies under normal conditions, in accordance with functional variations in the vessels and in the surrounding tissue. Under certain conditions however the filtration pressure may increase to such an extent that this rise may become a factor in the increased transudation and even lead to edema. This holds particularly good in regions where the blood-vessels possess normally relatively considerable permeability.

E. Calcium and edema

There exists an antagonistic action between the bivalent calcium and the monovalent sodium ion which is apparent in many physiological functions; while sodium tends to stimulate, calcium has an inhibiting effect.

According to Jacques Loeb and Osterhout this inhibiting action of calcium depends on a diminution in the permeability of the cell membrane which this ion produces. Sodium on the other hand increases this permeability. Osterhout assumes that calcium and sodium combine in definite proportions with a constituent of the cell, and that, according to the relative proportion in which these two combinations of the cell constituent, with either sodium or calcium, are present, the permeability of the cell varies.

R. Hoeber and R. S. Lillie especially referred the antagonistic action of sodium and potassium ions, on the one hand, and of bivalent ions on the other hand, to their effect on cell colloids. While the monovalent kations tend to exert a softening or dissolving effect, the bivalent

ions and particularly calcium have an opposite, hardening, coagulating effect on the cell colloids. Similarly Herbst has shown that without the presence of calcium salts the blastomeres of the echimoderm egg separate from each other, while they join again after addition of these salts.

In a somewhat different way Clowes explains the effect of calcium on the permeability of membranes. He found that addition of calcium chloride to an emulsion of oil in water tends to transform this emulsion into the reversed emulsion of water in oil. This change would necessarily lead to a decreased permeability of a membrane consisting of such an emulsion to substances soluble in water, but insoluble in oil.

These facts suggested the conclusion that calcium salts might exert an influence on edema. In 1896 A. E. Wright first proposed the use of calcium in the treatment of various hemorrhages and of urticaria, which latter represents an edematous condition of the skin. This author based his recommendation on the effect of calcium in the clotting of the blood. However, the first experiments dealing with the influence of calcium salts on the formation of transudates were to our knowledge carried out by Fleisher, Hoyt and Leo Loeb and by Fleisher and Loeb. We compared the effects of the intravenous injection of isotonic sodium chloride solutions on the one hand, with those of a mixture of four parts of this solution and one part of a calcium chloride solution on the other hand. In a very extensive series of experiments we found that calcium chloride diminishes the quantity of urine and of intestinal fluid, which are both augmented through the intravenous injection of sodium cloride solution. We could furthermore show that the effect of calcium on the kidney was not due, as had been maintained by Porges and Pribram, to a lowering of the blood pressure caused by the injection of this substance, but to a direct action on the kidney cells. This was proven in experiments in which we combined calcium chloride with adrenalin, which maintained the blood pressure at a considerable height and still we obtained the typical calcium effect. Similarly calcium affected the secretion into the intestines directly and not indirectly through the circulation, as experiments showed in which we compared the calcium action with the effect of an experimentally produced myocarditic lesion in rabbits; this latter

likewise causes a lowering of the blood pressure and a diminution in the amount of urine. The fall in blood pressure caused by the myocarditic lesion did not affect the amount of intestinal fluid. While thus calcium exerted a markedly inhibiting effect on the secretion of urine and intestinal fluid, it increased, on the contrary, very noticeably the transudation of fluid into the peritoneal cavity, and it increased also the incidence of pulmonary edema. This increase was found not only in normal rabbits, where calcium might cause a retention of fluid by diminishing the amount of urine and of intestinal secretion, and thus increase the amount of peritoneal transudate only indirectly, but it was manifest even in nephrectomized animals, where such an interpretation could not hold good.

We may thus conclude that the elimination of fluid into the peritoneal cavity follows laws altogether different from those governing the secretion through kidney and intestines. We could furthermore show through comparison of the effects of calcium chloride with those of myocarditic lesions that alterations in the blood pressure are not an important factor in the formation of the peritoneal transudate caused by intravenous injections of these solutions. In a similar way, while the absorption from the intestines is diminished by calcium, the absorption from the peritoneal cavity is not inhibited by this substance.

Furthermore according to our observations calcium chloride, in the proportions in which we added it to the blood, does not influence in a noticeable way the elimination of fluid from the blood-vessels, neither retarding nor accelerating it. On the other hand, after a preliminary rise it causes a marked fall in blood pressure. We may then conclude that calcium affects the amount of ascitic fluid in one of two ways: it either acts directly in a specific manner on the endothelial lining of the serous cavities, or it diminishes the storing of water in those tissues which normally act as reservoirs for water, especially the muscles and the skin.

In apparent contradiction to our results, which are based on a large series of concordant experiments, are the subsequent investigations of Chiari and Januschke. These investigators found that subcutaneous injections of calcium salts in rabbits, given previous to the application of mustard oil, prevents, or at least noticeably diminishes, the inflammatory edema following an application of mustard oil to the

conjunctiva. They also found that these salts prevent edema of the lung and the formation of pleural exudate, which result from the injection of diphtheria toxin and of sodium iodide.

As far as the influence of calcium salts on the formation of pleural exudates is concerned, the results of Chiari and Januschke could not be confirmed by subsequent investigators (R. Levy, H. Leo, Muller and Saxl). L. Pollak likewise found that calcium salts do not inhibit the formation of peritoneal transudate in rabbits poisoned by uranium nitrate. Neither does calcium seem to exert a decidedly beneficial therapeutic effect on the inflammatory edema caused by mustard oil, but on the other hand the prevention or mitigation of inflammatory edema by injections of calcium chloride previous to its onset has been confirmed by various authors (R. Levy, Heubner, Luithlen). Also the inflammatory exudate caused in the pleural cavity by local application of turpentine can be diminished temporarily through calcium; but on the second day this mitigating effect of calcium chloride has disappeared (R. Levy).

The action of calcium salts in this respect, however, cannot be very striking. Cushny, in repeating Chiari's and Januschke's experiments with mustard gas, obtained negative results, and, in agreement with Fleisher and Loeb, Bayliss found that an excess of calcium chloride added to Ringer's solution does not retard the elimination of the fluid from the blood-vessels. According to Sollmann a concentrated solution of calcium chloride applied intradermally not only does not prevent, but it even causes edema (urticaria). According to Laqueur and Magnus under certain conditions calcium chloride administered subcutaneously may, to a slight extent, diminish the pulmonary edema caused by inhalation of irritating gases, while after intravenous injection it may, on the contrary, increase edema, as our experiments have shown.

It is certain that calcium decreases the secretion of urine and increases the formation of transudates in normal animals, if injected intravenously. On the other hand, Maase and Zondek as well as E. Schultz observed that the acute war edema was influenced favorably by administration of this salt. W. Hülse finds furthermore that calcium salts given orally in large doses effect a rapid discharge of renal edemas in many cases, even when other means have been found

ineffective. It also influences the nephritic process beneficially. This author interprets this effect as due to the diminution in the water binding power of colloids, which is caused by bivalent kations.

It is not probable that these apparently contradictory statements are due to errors of observation. Calcium seems to exert various functions under different conditions. Its preventive effect on inflammatory edema may possibly be due to a constricting action on blood-vessels and to a decrease in permeability of the endothelium. Haffner observed that calcium chloride may cause an intense constriction of vessels—an observation which agrees with those reported in a preceding chapter—and according to Rosenow and Starkenstein it delays the absorption and elimination of fluorescin through the blood-vessels. This agrees also with the fact that Exner and Meltzer and Auer have shown that adrenalin causes a delay in absorption and that Rosenow observed that adrenalin acts similarly to calcium salts in inhibiting the formation of inflammatory exudate. Inasmuch as we know that adrenalin exerts its effect through causing constriction of the vessels, we may consider the possibility that calcium chloride acts similarly. In agreement with this fact is the observation that the action of calcium chloride in inflammatory edema is of a transitory character.

We have referred above to the observations of Günsburg and Hamburger on the effect of salt solutions on edema in perfused frogs. Hamburger has shown that Ca added in a certain proportion to a 0.6 per cent NaCl solution may prevent edema in the frog-leg, which a NaCl solution alone would produce. In a favorable proportion Ca may make the vessel wall less permeable and this effect is related to a contraction of the vessel which occurs under the influence of a slightly stronger solution. A sufficient supply of oxygen likewise decreases the permeability of the vessels and causes their contraction. These observations support then the view of the connection between a decrease in permeability and an increased contraction following an increase in Ca ions.

Now, while under certain conditions, if used in certain proportions, calcium may decrease the permeability and thus prevent edema, in other proportions it may perhaps have the opposite effect. Thus according to H. I. Hamburger calcium diminishes the permeability of the glomerulus epithelium for sugar, if used in medium concentra-

tion, but it increases it if used in larger or smaller concentration. It acts in a similar manner in hemolysis and certain other conditions. This might explain the apparent differences in our results and in those of Chiari and Januschke. It might also be that calcium affects the peritoneal endothelium and the vascular endothelium differently. As to the occasional beneficial effect of calcium in cases of renal edema, some additional explanations have been suggested. Thus it has been assumed that calcium may counteract the effect of sodium and in this way neutralize one of the important factors responsible for renal edema. Hülse suggests in addition that calcium may cause a disappearance of the spastic constriction of preglomerular vessels and thus make possible a better perfusion of the kidney with blood; or it may diminish inflammatory conditions in the kidney in cases of nephrosis and thus aid in the elimination of sodium chloride and water (Starkenstein). It is of course possible that in addition calcium chloride exerts an influence antagonistic to sodium chloride within the tissue.

In recent studies Blum, Aubel and Hausknecht interpreted the beneficial action of calcium chloride in renal edema as due to its effect on the elimination of sodium. Bunge had previously found that ingestion of potassium salts leads to an increase in the excretion of sodium through the urine. These authors confirm Bunge's conclusion and extend it to calcium, which likewise increases the elimination of sodium through the kidney. Now, according to Blum, the current of water always follows the movement of sodium. Therefore elimination of the sodium leads to a discharge of edematous fluid. In this manner calcium chloride diminishes the sodium content of the blood and prevents the latter ion from migrating from the blood into an area of inflammation and at the same time drawing with it a current of water. In a similar manner they explain the experiment of Chiari and Januschke on the effect of calcium in preventing the inflammatory edema caused by instillation of mustard oil.

In case the kidney is not very permeable to sodium, calcium and potassium may have the opposite effect, causing an increased elimination of sodium into the ascitic fluid. Calcium and potassium salts would thus not only not decrease the amount of edematous fluid, but on the contrary increase it. However, inasmuch as it has not yet been shown that the effects of calcium and potassium run a parallel course, this explanation is still hypothetical.

As to the mechanism by which calcium chloride leads to the elimination of sodium, another explanation has recently been suggested by Frey. He assumes that after administration of calcium chloride the calcium is principally eliminated through the intestines, while the anion is excreted through the kidney and draws with it the sodium ion, thus leading to the discharge of the latter.

But the fact that intravenous administration of a calcium salt leads to the discharge of the edematous fluid even in cases of cardiac decompensation and in cardiorenal disease, suggests that calcium may under these conditions act in a way similar to digitalis, strengthening the heart action, diminishing the frequency of the pulse and lowering the blood pressure (Singer). It would therefore cause the discharge of the edematous fluid in a manner similar to digitalis, namely, through removal of those circulatory defects which were responsible for the origin of edema under these conditions.

We have evidently to deal with an interaction of different mechanisms. This seems the more probable, as we know that the effect of calcium on inflammatory edema is not strictly specific. We have mentioned above that anesthetics may have a beneficial effect and a similar effect is exerted by adrenalin. In addition Januschke found that magnesium sulphate likewise may prevent inflammatory edema, even in doses which are not large enough to cause anesthesia.

The effects of calcium are then as follows: Calcium salts administered intravenously may increase the amount of transudates in animals. The mechanism through which calcium influences the formation of urine and intestinal fluid, differs therefore from that through which it influences transudation. It may diminsh the permeability of the blood-vessels and cause their contraction under certain conditions and may thus prevent the inflammatory edema following the local application of certain irritating substances. This effect is, however, not strictly specific. Calcium has no curative effect, once the inflammatory edema has been produced. It does not diminish the amount of inflammatory transudates in the serous cavities, nor does it noticeably influence the transudation of fluid through the blood-vessels. However, in a manner similar to potassium salts, calcium salts may, in certain cases of renal or cardiac edema, lead to a discharge of edematous fluid. The mechanism through which this

latter calcium effect is accomplished is as yet doubtful, but it may be that the action is an indirect one and that it is due to the acceleration in the elimination of sodium following the administration of calcium; or in case of cardiac or cardiorenal disease, it may be due to an improvement of the circulation.

Calcium is furthermore necessary to balance the effect of sodium on the permeability of the blood-vessels. Too large a proportion of sodium or potassium chloride increases the permeability of the blood-vessels while calcium added in a certain proportion counteracts this effect.

F. Conclusion

Recent studies of the circulation, especially of the capillaries, bring evidence that the permeability of these vessels is a variable factor which in some way runs parallel to their state of dilatation in response to functional as well as pathological conditions, and that pathological stimuli may cause a still further circulatory change and may in particular call forth an increase in the capillary permeability. This permeability is a graded one permitting elements of different sizes to pass through the vessel walls. Thus colloid particles of various sizes may leave the vessel wall and fill the interstitial spaces around the vessels. All the evidence points to the conclusion that these changes in vascular permeability are important factors in various kinds of edema, primarily in those of a localized character, but they play probably a similar rôle in some generalized edemas. Related conditions exist in shock, where a state of frustrated or abortive edema exists; however, the character of shock, being a transitory condition, precludes the development of a renal edema. In certain of these acute circumscribed edemas, hereditary factors may play a part.

III. GENERALIZED EDEMA DUE TO DEFECTIVE CIRCULATION; EDEMA IN CARDIAC DECOMPENSATION

The edema found in cardiac decompensation is due to factors which obstruct the return of the venous blood to the heart. Secondarily there may be added to this direct circulatory effect interference with the function of the kidneys. The main problem which we have to consider concerns the way in which venous obstruction causes edema

and this leads back to the theories of lymph formation. The teaching of Ludwig, that filtration pressure in the blood-vessels is mainly responsible for the formation of lymph, was sustained especially by the experiments of Starling. In addition the latter assumed that in places of lowered blood pressure the excess of osmotic pressure in the blood-vessels, due to the presence of a surplus of protein in the blood, causes a return of the fluid into the capillaries. To these factors, present in a quantitatively abnormal manner, Starling attributed cardiac edema. Cohnheim emphasized as a further factor an injury of capillary walls due to malnutrition. According to these views then cardiac edema is due to the rise in capillary and venous pressure, and to the resulting increase in filtration combined with a lowered ability of the vessels to reabsorb the fluid, owing to the hydremic character of the blood which has become less potent osmotically. In addition the increased permeability of the injured vessels permits a greater amount of fluid to filter out of the blood-vessels. Those authors who attribute the transudation of fluid from the capillaries into the tissue mainly to an increase in intracapillary blood pressure, interpret likewise the microscopic changes observed in the frog circulation in cases of venous obstruction as due to filtration of fluid (Klemensiewicz); they point furthermore to the watery condition of the lymph in passive congestion and assume that, whether or not edema follows, increased filtration pressure depends upon the facilities which exist for the elimination of the excess fluid which has passed into the tissues. As to this latter condition, again mechanical factors play a preponderating rôle according to these conceptions. Wherever the tissue shows a dense structure, the fluid is pressed back primarily into the blood-vessels; only in loosely built tissue does an accumulation of fluid readily occur. Thus in the experiments of Ludwig and Thomas ligation of the plexus pampiniformis led to an edema of the loose tissue surrounding these veins. The lower eyelid likewise is a favorite seat for renal edema on account of the looseness of the structure of this tissue. In venous thrombosis and cirrhosis of the liver obstruction to the outflow of blood may also lead to edema through similar mechanisms.

While all these considerations suggest that such mechanical factors may play a part, still even several of the older experiments tend to

prove that other factors must be combined with increased filtration pressure if edema is to result. Thus arterial hyperemia due to vasomotor paralysis, when added to obstruction to the venous outflow, may produce edema, though either of these two procedures alone would prove ineffective. Cohnheim showed that the cutting of the cervical sympathetic nerve in the rabbit and a simultaneous tying of the large vein of the root of the ear will produce edema of the ear of the rabbit, while such an effect cannot be produced through a cutting of the sympathetic alone; a cutting of both the sympathetic and the auricular nerves, which increases the vasodilatation, will however also have this effect. Similarly a ligation of the femoral vein in the dog does not lead to edema, owing perhaps to the establishment of collateral channels of circulation; but if the tying off of the femoral vein is accompanied by a cutting of the sciatic nerve, the principal vasomotor nerve of the leg, edema will result.

On the other hand, there are facts which make it possible that even in cases in which variations in blood pressure, tissue pressure, and filtration were assumed to be the principal causes of an increased transudation, other factors, and especially variations in the permeability of the capillary wall, play an important rôle. Thus, for instance, the experiments of Asher and Boehm on the effect of adrenalin on transudation, suggest that filtration may play a more subordinate rôle than had been assumed, even in conditions in which mechanical factors suggested themselves primarily.

The more recent observations concerning the permeability of the capillaries, to which we referred in the preceding chapter, render it likewise very probable that while we cannot exclude the possibility that increase in blood pressure may be a factor in the surplus transudation of fluid into the tissue which leads to edema, an increased permeability of the capillaries, associated with their dilatation, may be a factor also, and an important one, in the formation of edema, even in cases in which the capillary blood pressure is increased.

It is assumed by many authors that the malnutrition of the capillary endothelia and of the surrounding connective tissue in cases of cardiac decompensation increases the permeability of the vessels for water, salts and even proteins, and that these substances thus accumulate in the interstitial tissue surrounding the capillaries. It

appears that non-protein nitrogen also is retained in the tissues in certain cases of severe cardiac decompensation accompanied by deficiencies in kidney function (O.Kleine). Such an injury of the capillary vessels might be due to a disturbance of the acid base equilibrium in the blood and tissue through a lack of oxygen. A lack of oxygen in the venous parts of the capillaries and in the veins may be produced in two ways: (1) through a deficient oxygenization of the blood in the lung, and (2) through an increased use of oxygen as a result of the slowing of the capillary circulation. Both play a part, in varying degrees, in different kinds of cardiac lesions, as especially Lundsgaard has shown in quantitative determinations. There may in addition be a deficiency in arterial oxygen, if the pulmonary gas exchange is very faulty (Harrop). To some extent this deficiency in the supply of oxygen is counteracted by an increased minute volume of inspired air. This factor as well as the increased elimination of oxygen from the capillaries may lead to an increase in basal metabolism in cases of cardiac decompensation (Peabody,Wentworth and Barker). Yet this compensatory process does not necessarily safeguard against a lack of oxygen in the venous component of the capillaries and deficient nutrition of certain capillary connective tissue areas might result, despite an increase in oxygen consumption. In addition a deficiency in proteins which has been recorded in the blood in cardiac decompensation might lead to malnutrition of the vessels and the surrounding tissues. While we have thus to take into account the possibility of injury to the vessel wall, yet the actual proof that these factors do cause abnormalities in the interchange of substances between vessels and surrounding tissue has so far to our knowledge not been given.

With the view that factors other than increased filtration pressure may play a part in the edema accompanying venous obstruction, the studies of Bolton agree as to the mechanism of cardiac edema, which he produced through partial constriction of the inferior vena cava. He finds that edema, which develops within a few hours after the onset of the obstruction, is independent of a rise in capillary pressure. It depends instead upon a venous and capillary congestion, accompanied by a distention of the capillary and venous channels and by a slowing of the blood flow. This leads to an increased transudation of fluid

from the vessels, which is accompanied by a diminished reabsorption; it is thus associated with an increased flow of lymph. In addition there develops a hydremic plethora in the vessels, due to an increased absorption of fluid at points of the circulatory system where the capillary pressure is lowered, and due also to secondary changes in the kidney function. This condition tends still further to increase the transudation of fluid and the amount of edema. The hydremic plethora is subsequently transformed into a true plethora in consequence of a new formation of erythrocytes. The edema may increase for a period of several weeks, but it disappears as soon as blood-vessel anastomoses have been established; the latter lead to a more rapid circulation of the blood and with the cessation of stagnation the increased transudation and the lowering of the absorption of fluid from the tissues into the blood come to an end. Bolton hesitates to assume that a structural damage is inflicted on the capillary walls as the result of malnutrition, considering the rapid improvement which takes place with improved circulation.

While the experimental procedures used by Bolton cause an acute venous obstruction, it is possible to produce experimentally in the rabbit a state in which the heart acts normally under the usual conditions, but an inferiority of the heart action becomes apparent as soon as excess work is required. Fleisher and Loeb produced myocarditic lesions in rabbits by a single intravenous injection of a combination of adrenalin and spartein or caffeine. This procedure is followed in a considerable number of animals by structural alterations especially near the auriculo-ventricular groove, and, as Christian, Smith and Walker have shown, it may even lead to endocardial alterations. Such a heart works apparently well under usual conditions, but if intravenous infusions of solutions of sodium chloride or of a combination of sodium and calcium are made, the heart is not equal to its task; the blood pressure is lowered, more fluid is retained within the vessels, and, as the result of these circulatory changes, the amount of urine secreted is diminished. On the other hand the quantity of peritoneal transudate and of intestinal fluid produced is not thereby noticeably altered. It seems then that the formation of intestinal fluid is to a greater extent independent of vascular changes than the formation of urine. The further experiments of Fleisher and Loeb

on the inability of adrenalin to affect the intestinal fluid are in agreement with these results. While therefore under these experimental conditions the heart lesion does as yet not lead to edema, still it permits us to imitate experimentally the circulatory conditions which prepare the way for the development of edema. It seems, however, that in animals in which myocarditis has thus been produced experimentally, the liability to the formation of pulmonary edema is somewhat increased. We believe that this method may prove useful in the further analysis of cardiac edema.

In addition to an increased transudation a decreased absorption of fluid from the tissue spaces plays a part in the development of cardiac edema. Thus in persons suffering from decompensated heart disease and subsequent edema, Reichel observed a delay in the absorption of fluid injected subcutaneously. F. Kauffmann found a delay in the absorption of injected fluid from the subcutaneous tissue even in patients suffering from compensated heart disease without a visible edema. This author furthermore states that in patients who are in a state of pre-edema, and in whom a retardation in the excretion of fluid and a retention of fluid in the intercellular spaces, especially of the lower extremities, occur, although this retention is not yet visible to the naked eye, elevation of the lower extremities causes an increased elimination of the fluid and an increased diuresis. In such pre-edematous cases the weakening of the circulation leads to a slowing of the blood flow through the lower extremities, with both a subsequent retardation in the absorption of fluid into the capillaries from the subcutaneous spaces and an increased elimination of fluid from the blood into the tissue spaces. An improvement in the circulatory conditions counteracts this effect. If, on the other hand, edema is once well developed, this procedure ceases to be effective.

We may conclude that an increase in the amount of interstitial fluid, a condition of pre-edema or of latent edema, exists even in certain cases of apparently compensated heart disease; but the movement of water from the capillaries to the surrounding fluid is here quantitatively weaker and thus there results merely an invisible edema. We are accustomed to conceive of edema a well fixed entity. Instead we have probably to deal with a process of a continuously increasing character. When a certain limit has been reached in this abnormal

process, we speak of edema. This consideration applies in all probability to all kinds of edema, including those of a renal origin.

It holds also in conditions in which a local slowing of the circulation exists as, for instance, in case of varicose veins in the lower extremities. Here too all degrees of retention of fluid in the interstices of the connective tissue exist from apparent normality to distinct local edema in the dependent parts of the body. In many other conditions a latent retention of water exists; it has been observed in pneumonia (Schwartz). Yet to our knowledge no systematic attempt has been made so far to analyse these minor disturbances in the retention of water and salts.

A somewhat related condition, in which an experimentally produced obstruction to the blood flow led to a retardation in the absorption of fluid and to subsequent edema, seems to have been realized by Galeotti, who injected into a dog intravenously a hypertonic solution of sodium chloride or sugar after the crural vein had previously been ligated. While under normal conditions the hypertonic transudate which enters the tissue spaces from the blood-vessel would rapidly be absorbed, absorption in such a case is retarded as a result of the circulatory disturbances. Consequently the hypertonic transudate remains for a longer period in the tissue spaces, attracts fluid from the surrounding sources of water supply, and thus edema develops. Whether, as Galeotti suggests, an increased transudation under the influence of the hypertonic salt solution is the cause of edema in this case is doubtful. This experiment is also instructive as a further illustration of the fact that several factors, which, when acting singly, are ineffective, may when acting in combination be sufficient to call forth edema. It is then probable that associated with the increased transudation in heart disease there is a retardation in absorption responsible for the development of edema.

Not only do we find a delay in the absorption of fluid but also a retention of sodium chloride in cases of cardiac edema and in this respect the latter resembles renal edema. Vaquez and Digne observed a retarded elimination of sodium chloride even in cases of compensated heart disease. Barantschik likewise found a retardation in the excretion of an excess of NaCl given with the food, a retardation which is independent of a kidney lesion. If an excess of sodium chloride

is given, without a corresponding amount of water, a dry retention of sodium chloride may occur with or without an accompanying edema. Such a dry retention may also be followed by edema and a subsequent excess elimination of NaCl, which surpasses the amount of this salt usually eliminated in a corresponding quantity of edematous fluids.

Strauss states that a hydremia, as determined by the refractometer, occurs only in severe cases of cardiac decompensation. Veil also and other authors find occasionally a hydremic plethora in cardiac decompensation. According to Beckmann the condition which we find in the blood depends upon the degree of saturation of the tissues with water. If the tissues have become saturated with water, a back flow of water to the blood takes place and thus the blood becomes more diluted. In later stages of the disease, on the other hand, sometimes an inspissation of the blood has been observed (Loeper and Cheray and others). Heineke finds that if diuresis takes place in cases of cardiac edema, first a dilution of the blood occurs and subsequently an increased concentration. Part of the edematous fluid is discharged through increased perspiration. These observations suggest that the state of the tissues plays a certain rôle in cardiac edema. In the same direction perhaps points the following experiment of Nonnenbruch: In passive congestion and edema of cardiac origin, water given by mouth is retained, but given intravenously it is excreted—a condition which is the reverse of that found in normal dogs. According to Nonnenbruch this result indicates that the kidney is able to excrete water and sodium chloride and that it merely fails to do so because the tissues retain the fluid. It might, however, be that in cases of cardiac decompensation water given intravenously is excreted more rapidly, because in this case the constitution of the blood is temporarily changed much more rapidly than if the fluid is given by mouth. In the latter case the alteration in the composition of the blood might be too slight to act as a stimulus. As to the existence of plethora, the findings of Bock seem to contradict the conclusions of those authors which assume the existence of a real plethora in heart disease. With the vital red method Bock noticed no change in the quantity of the blood plasma in heart disease.

On the whole the concentration of sodium chloride in the blood in cases of cardiac decompensation and edema seems often to be low (Veil, V. Monakow, Bauer). Probably this substance enters the transudate and the tissues and is here retained; in other cases, however, its concentration in the blood may be normal. Veil states that a hyperchloremia, similar to that found in certain kidney diseases, does not occur in heart disease. Yet it seems that certain variations in the sodium chloride content of the blood do occur in heart disease and that in some cases the concentration of this substance in the blood may be increased, especially at the time when the edema begins to form, or at the time of its disappearance.

A salt free diet may lead to a dilution of the blood, owing to the movement of the water from the tissues to the blood and thus to an elimination of the fluid which may take place partly through other channels than the kidney (Heineke). But while changes in the elimination and distribution of sodium chloride are in cardiac edema on the whole similar to whose in nephritic edema, the significance of these factors does not seem to be so marked in cases of cardiac as in cases of renal edema. In the former withdrawal of sodium chloride from the diet does not lead to so rapid a discharge of the edema as in the latter, nor addition of this substance to so marked an increase in the quantity of the retained fluid (Magnus-Levy).

In addition to abnormalities in the distribution of sodium chloride, there may also be a retention of other substances in cases of cardiac decompensation. Thus an increase in the non-protein nitrogen in the blood is found, although only in extreme cases of cardiac decompensation, or when a decompensation of a medium intensity has lasted for a longer period of time, a condition which usually is associated with oliguria (Otto Klein); it may be the latter which is mainly responsible for this increase of non-protein nitrogen.

Summary

Dilatation of the capillaries and veins due to the faulty functioning of the circulation is the principal cause of the increased transudation and the subsequent edema in cardiac decompensation, but there may perhaps be in addition an increased filtration pressure responsible

for these results. The vascular dilatation is apparently followed by an increased permeability of the capilllaries and by a movement of sodium chloride and water in the direction from the blood to the tissues. Retention of sodium chloride plays a rôle also in the case of cardiac edema, although it is a smaller one than in the case of renal edema. In certain stages of cardiac edema a hydremia seems to occur. As to the occurrence of a true plethora, the statements are contradictory. In addition to the increased transudation, there is a delayed absorption and an alteration in the relations determining the exchange of fluid between tissues and blood-vessels. Experimentally produced myocarditic lesions may give rise to a lowering of blood pressure and a diminution in the amount of urine under certain conditions, but so far it has not been possible to influence by this experimental method the amount of edematous fluid.

IIIa. DECREASED EXTRAVASCULAR PRESSURE AS CAUSE OF EDEMA

In certain cases a localized edema is caused by an absorption of tissue provided the cavity thus produced is not filled in by the surrounding tissues. Thus atrophy of the brain, which is surrounded by a bony, unyielding capsule, may lead to edema; atrophy of fat may in certain cases have a similar effect. The transitory edema following cupping represents an acute condition of the same character.

In these cases a mechanical factor, a disparity between intravascular and tissue pressure, seems to be the cause of the edema.

IV. THE INFLUENCE OF ADRENALIN ON THE FORMATION AND ABSORPTION OF TRANSUDATES

In order to separate the various factors which may be responsible for edema, it is not without interest to study the effect of substances with some well defined physiological actions like adrenalin in the development of edema. Adrenalin causes a constriction of arteries and capillaries and raises the blood pressure. In small doses it may dilate the capillaries; furthermore in certain organs the action of adrenalin on the blood-vessels seems to be generally that of dilatation. It retards the absorption of certain substances parenterally introduced and their elimination into the blood-vessels (Exner, Meltzer and Auer).

In recent experiments Embden and his collaborators (Kauffmann, Lange) found that adrenalin retards the exchange of substances through a membrane consisting of frog skin as well as the entrance of substances into the muscle and the passing of substances out of the muscle. In this case adrenalin affects the membrane lining the muscle fibers in a manner similar to frog-skin and blood-vessel wall. The effect of adrenalin in diminishing the permeability of membranes seems therefore a general effect and in this respect it resembles calcium chloride. In both of these substances the diminution in permeability of membranes goes hand in hand with a contraction, provided the membrane contains contractile elements. It is probable that to this effect in decreasing the permeability of the capillaries is due the retarding influence which adrenalin may exert on the development of inflammatory edema, as for instance, the edema caused through instillation of mustard oil in the conjunctiva of rabbits.

If injected in a large quantity intravenously into rabbits, adrenalin causes an acute edema of the lungs. On the other hand, the slow, continuous intravenous injection, extending over a period of twenty minutes, leads to a rise in blood pressure in the somatic as well as in the splanchnic areas; it impedes the circulation in the liver and causes an increased lymph flow (Bainbridge, Trevan, Erlanger and Gasser). Hess, Erb and Lamson found that an injection of a larger amount of adrenalin is followed by passing of fluid out of the vessels; the blood is thus made more concentrated.

It is usually assumed that this change in composition of the blood is due to a filtration process; the result of the increase in blood pressure under the influence of adrenalin. In accordance with the findings of Bainbridge and Trevan, Lamson refers it to the obstruction which develops in the capillaries of the liver after injection of adrenalin. This is supposed to lead to an increased transudation of fluid into the lymph vessels of the liver. On the other hand in a recent study F. O. Hess finds that following injection of adrenalin, the number of erythrocytes is increased only in the arterial, but not in the capillary blood. He is therefore inclined to attribute the increase in the number of red corpuscles not to a movement of fluid out of the blood-vessels, but to a mechanical alteration in the distribution of the erythrocytes within different parts of the vascular system. Asher and Böhm

attribute the alteration in the composition of blood to an increase in organ activity caused by adrenalin. They are led to this conclusion because they find that an increase in blood pressure caused by mechanical measures does not result in an increase in concentration of the blood, an observation which agrees with the results of Lamson.

Fleisher and Loeb studied the effect of an addition of very small amounts of adrenalin to a solution of sodium chloride to which had been added a certain proportion of calcium chloride, the adrenalin flowing continuously into the jugular vein of a rabbit during a period extending over several hours. Under such conditions adrenalin leads to a continuous rise in blood pressure which lasts several hours. Only towards the end of the experiment a steep fall in blood pressure occurs, if calcium chloride has been added to the fluid, while with a pure solution of sodium chloride the blood pressure remains elevated throughout the experiment. The apparent pressing out of fluid from the vessels, which is noticeable after application of adrenalin over shorter periods of time, is not observed under these conditions. A certain increase in the concentration of the blood occurs, however, if adrenalin is injected intravenously in repeated doses, or if it is injected intraperitoneally together with a solution of sodium chloride; under such conditions a larger amount of adrenalin enters the blood-vessels in a unit of time than when this substance flows in continuously in very small quantities; if it is injected by the latter method through the jugular vein mixed with a solution of sodium chloride, it increases the amount of urine, leaves unchanged or diminishes the amount of intestinal fluid and increases the amount of peritoneal transudate. As far as the formation of urine is concerned, adrenalin and calcium chloride act antagonistically, but the effect of calcium chloride proves stronger in a mixture of sodium chloride, calcium chloride and adrenalin, and the amount of urine is diminished, but is still larger than if the calcium chloride and sodium chloride alone are used. The lowered secretion of urine results under those conditions notwithstanding the continued rise in blood pressure. The diminution of the intestinal fluid, which occurs under the influence of calcium chloride alone, is not markedly affected through the admixture of adrenalin. As to formation of peritoneal transudate, a summation of the effects of calcium chloride and adrenalin takes place and the amount of fluid

eliminated into the peritoneal cavity under those conditions is much increased. We find thus a tendency of adrenalin to increase the amount of fluid eliminated either into the peritoneal cavity or through the kidney and these effects run parallel to the rise in blood pressure caused by adrenalin. This increase in peritoneal transudation persists even in nephrectomized animals, and it is therefore not dependent on the function of the kidney.

Equally definite is the effect of adrenalin administered intraperitoneally or intravenously in increasing the absorption of fluid from the peritoneal cavity (Fleisher and Loeb, A. J. Clark). This is contrary to what might have been expected considering the experiments of Exner, Meltzer and Auer, who found that adrenalin retards the movement of substances through capillaries. This increase in absorption of peritoneal fluid is independent of the osmotic pressure of the fluid injected intraperitoneally. At the same time adrenalin augments also the absorption of sodium chloride from the peritoneal cavity. In case distilled water is injected intraperitoneally adrenalin diminishes the passage of sodium chloride from the blood into the peritoneal cavity and the sodium chloride concentration of the peritoneal fluid. This agrees also with the observations of Achard and Caillard in guinea pigs. In some cases adrenalin increases not only the total amount of sodium chloride which is absorbed from the peritoneal cavity, but it increases the absorption of this substance relatively more than that of water, and there may thus still be an increased absorption of sodium chloride from the peritoneal cavity in cases in which the absorption of water is no longer increased through adrenalin, as in nephrectomized animals or in animals which have been injected with uranium nitrate three days previously. As early as one day after administration of uranium nitrate, on the other hand, the absorption of fluid from the peritoneal cavity and the secretion of urine are still increased by adrenalin. We can explain the effect of adrenalin on absorption of fluid through its effect on the osmotic pressure of the blood, which we found raised under the conditions of our experiments, following administration of this substance. This increase in osmotic pressure leads to an increased absorption of water from the peritoneal cavity. When on the other hand the osmotic pressure of the blood is already raised previous to the injection of

adrenalin, as is the case in animals nephrectomized or operated upon otherwise, or injected with uranium nitrate three days previously, adrenalin no longer influences the absorption of fluid from the peritoneal cavity, but it may still accelerate the absorption of sodium chloride. At the same time there seems to be a connection between the action of adrenalin on the kidney function on the one hand, and its effect on the absorption of transudates on the other hand. The influence of adrenalin on the passage of water and dissolved substances from the blood-vessels into the tissues may also be a factor which determines the effect of adrenalin on the distribution of fluid in the body. The increase in the amount of ascitic fluid under the influence of intravenously injected adrenalin, is explained probably by the peculiar change produced in the circulation of the liver, by this substance (Bainbridge and Trevan, Erlanger and Gasser). There are certain similarities existing between the effects of calcium chloride and adrenalin; both retard the passage of substances through membranes and cause a contraction of blood-vessels, if used in certain concentrations, and both may prevent certain inflammatory symptoms; at the same time these substances increase the amount of fluid eliminated into the peritoneal cavity after intravenous injection of salt solutions.

Summary

We find adrenalin a substance which affects in a definite way the distribution of edematous fluid and of sodium chloride. We have shown that at least a part of these effects is secondary to osmotic changes which are produced by adrenalin. It has furthermore been shown that adrenalin affects the permeability of membranes. How far in addition localized changes in blood pressure play a part in this process, cannot be stated definitely at the present time. It is however of interest that two substances as diverse as adrenalin and calcium chloride show similar effects on the distribution of fluid and dissolved substances; both decrease the permeability of different kinds of membranes for water and lead to a contraction of vessels, if used in certain concentration, and both increase at the same time the amount of ascitic fluid.

V. EXPERIMENTAL EDEMA IN EMBRYOS AND IN ADULT AMPHIBIA

McClure produced edema in frog larvae by exposing the embryos at an early stage of development to various injurious influences which prevented the normal formation of the pronephros tubules. In consequence of this interference the fluid which otherwise would have left the body as glomerular filtrate was retained in the body cavities. Similar conditions can be produced through bilateral extirpation of the pronephros in amphibian larvae (Swingle, Howland). Unilateral removal does not seem to have the same effect. In adult frogs also ligature of the ureters or cloaca produces edema (Overton). In these cases edema seems to affect mainly the large body cavities, but to a less extent also the subcutaneous tissue. Here it starts around the skin wound and gradually extends into the anterior region of the body. Recently E. Pohle confirmed the results of Overton in adult frogs. Extirpation of the kidney produces an increase in the amount of peritoneal fluid; it does not cause, however, a filling of the lymph sacs nor edema of the interstitial tissue of the skin.

E. L. and E. R. Clark showed that while interference with the blood circulation leads mainly to a collection of fluid in the body cavities, procedures which interfere with the development or function of the lymphatics in amphibia produce a much more generalized edema. The same effect of the lymphatics can be observed in chick embryos. The elimination of fluid in these organisms appears therefore to be effected principally through the lymphatics.

In edematous larvae the tissues proper in which the interstices are filled with fluid show signs of degeneration; they become vacuolar (Howland). This is presumably due to a secondary interference with the nourishment of the edematous parts of the body. It is very probable that the edema thus produced experimentally in larvae is to be attributed to mechanical factors, which lead to an insufficient elimination of fluid and the latter is then held back in the skin or in the body cavities.

Toxic conditions also may lead to edema in amphibian larvae; this has, for instance, been observed in salamanders which have been fed with thymus gland (Uhlenhuth). In this case circulatory disturbances also may possibly play a part, inasmuch as a slowing of the circulation is noticeable in larvae brought up on such a diet.

We see then that it is possible to produce edema in organisms representing somewhat more primitive stages of ontogenetic or phylogenetic development, by relatively simple means which interfere with the elimination of fluid. This is perhaps due to a greater intake of fluid in proportion to the body volume; or possibly the lack of certain regulatory mechanisms which come into play in higher forms may be responsible for this result.

VI. OBSTRUCTION TO THE LYMPHATIC CIRCULATION AS A CAUSE OF EDEMA; LOCAL DIFFERENCES IN THE FORMATION AND ELIMINATION OF INTERSTITIAL FLUID

In the preceding chapter we referred to the experiments of E. L. and E. R. Clark, who showed that procedures which interfere with the development or function of the lymphatics in amphibian larvae, produce a much more generalized edema than does interference with the blood circulation. Similar results have been obtained in chick embryos. These observations suggest that obstruction of the circulation of lymph may quite generally be a factor in the origin of edema, but that in higher organisms compensatory mechanisms may retard or prevent its appearance.

Older experiments, in which the effect of obstruction of the lymphatic circulation as to the production of edema was tested, gave contradictory results. While Cohnheim was not able thus to produce edema, according to Boddaert (cited by Meltzer) edema may result provided the obstruction to the lymphatic outflow is complete. The latter seems the more probable conclusion.

There are also more recent observations which favor this conclusion. Thus Volhard produced edema in the legs of frogs, in which arterial and venous circulation was maintained, while the lymphatic circulation had been obstructed through compression. This author explains this edema as due to interference with the return flow of lymph. Chronic edema may follow occlusion of lymph channels by filaria or their ova. This obstruction to the lymph flow and the resulting edema often lead in addition to connective tissue proliferation and elephantiasis. Opie observed, in cantharidin poisoning, edema of the liver, which he attributed to occlusion of the lymph

sinuses in lymph glands serving as channels for the hepatic lymph. In a case in which a carcinoma of the stomach caused widespread embolic metastases in the lymphatic vessels, which obstructed the lymph flow, extensive edema developed, at a time when the blood circulation was still good and cachexia absent (Schierge). We may assume that the obstruction to the outflow of chyle and lymph proper forced these fluids back into the serous cavities and interstitial tissue. Whether or not in order to obtain such positive results secondary factors must be active, in addition to this preliminary obstruction to the circulation of the lymph, cannot be definitely stated at the present time. If Cohnheim was unable to produce edema through ligation of lymphatics in the dog, it is possible that in these experiments the obstruction to the lymph flow had been incomplete and that the activity of the venous capillaries compensated for the deficiency in the effectiveness of the lymphatics.

In addition to a direct influence on the formation of edema, obstruction to the lymphatic circulation may render more difficult or prevent the absorption and elimination of edematous fluid, which has accumulated as the result of other pathological conditions; thus it may come about that a partial elimination of the edematous fluid by therapeutic means may be followed by a more complete elimination, owing to the freeing of the lymph circulation from the obstruction which was caused by the pressure of the edematous fluid.

In this connection we may state that it is believed that the blood-vessels represent the most important channels of absorption of the interstitial fluid. There is however reason for assuming that the lymph vessels also may participate in this process of absorption, although the extent of this participation does not seem to be definitely known at the present time.

The experiments on edema in embryos and in adult frogs, which we mentioned, indicate that here edema can be produced under conditions which would not lead to edema in normal mammals. There exist thus differences between different kinds of organisms in the readiness with which edema develops. But certain variations we find even in the mammalian organism, in the readiness of different tissues to become edematous. Thus while in general plethoric hydremia produced through intravenous injection of sodium chloride

solution does not produce edema of the interstitial tissue (Cohnheim and Lichtheim), it may have this effect in the connective tissue around the salivary glands, pancreas and the large vessels of the neck. This localized predisposition to edema does not depend upon organ activity, because it is also found around denervated and inactive glands (Wertheimer and Battez). In all probability it is caused by structural peculiarities which exist in the relations between the vessels and the connective tissue of various regions. Furthermore, it has been found that in the case of edema surrounding the salivary gland, for instance, that the activity of the gland itself may lead to a withdrawal of water from the interstitial edematous fluid and to its transport into the gland duct. This does not however occur if the gland has been made inactive through denervation or through the application of atropin (Wertheimer and Battez). There may be thus a third way of direct elimination of edematous fluid from the tissue spaces, through certain glands in addition to the usual route through blood and lymph channels. The choroid plexus may perhaps act in a similar way.

VII. EDEMA OF THE LUNG

The circulation and structure of the lung show certain peculiarities which make advisable a separate discussion of edema of this organ. There is an anatomical difference between pulmonary and the ordinary interstitial edema. In the former the edematous fluid not only fills the connective tissue spaces of the lung tissue, but usually also the alveolar air spaces which are lined by epithelium. In addition there seems to occur a pseudo-edema of the lung, due to a hypersecretion of bronchial and tracheal glands, which is followed by a movement of the secreted fluid into the air spaces; however, this is an effect which we do not need to consider. The real edema of the lung may be induced by many conditions which do not greatly differ from those found in other regions. There are, however, certain causes of edema which are peculiar to the lung, the main ones being as follows: (*a*) The terminal edema of various diseases may be limited to the lung. (*b*) Acute pulmonary edema may result from the inhalation of certain gases and also from certain other substances (like iodine, morphine, muscarine), even if they reach the lung merely by way of the circula-

tion. (*c*) Acute pulmonary edema may follow a sudden occlusion of the air spaces due apparently to a mechanical sucking of fluid from the circulation into the air spaces. (*d*) Edema of the lung and pleura may follow inflammation, here as elsewhere. (*e*) Edema restricted to the lung alone may occur in diseases of the circulatory system and of the kidneys. (*f*) It has been found furthermore in some skin affections, which are associated with an abnormal permeability of the capillaries, and lastly (*g*) pulmonary edema has been observed in certain nervous diseases.

Experimentally the main interest has attached to attempts to produce pulmonary edema through interferences with the circulation in the lung and through inhalation of poisonous gases. Welch obstructed the pulmonary circulation by various means and was able to produce edema of the lung only when obstruction to the outflow of blood from the lung tissue became very intense.

It is evident that in the usual clinical cases of pulmonary edema such an intense obstruction to the flow of blood does not exist. A similar condition however can be experimentally produced through intravenous injection of adrenalin in rabbits. We shall refer to this kind of edema again. Welch assumed that even without such a marked degree of obstruction, pulmonary edema may be caused by a disproportion between the working power of the left and right ventricle, in consequence of which the left heart is unable to expel in a unit of time as large a quantity of blood as is expelled by the right heart, provided the resistance to the movement of blood in the peripheral circulation remains unchanged. As Meltzer observes, the edema following intravenous injection of a large dose of adrenalin is in all probability due to a great rise in systemic blood pressure, which obstructs the outflow of blood from the left heart, while that from the right ventricle continues. It would therefore represent an extreme case of a disproportion between the working of the two sides of the heart. With this interpretation of the acute pulmonary edema produced in rabbits through adrenalin, the finding of Schaefer and Lun is in agreement, according to which adrenalin causes a much more significant rise in the systemic than in the pulmonary arterial pressure. Miller and Mathews point out that the pulmonary edema consequent upon administration of iodides also conforms to Welch's explanation,

and Hallion and Nepper apply it likewise to the edema following over-exertion and excitement, with subsequent rise in blood pressure, in cases of nephritis and insufficiency of the left ventricle. According to Matsuoka in beri-beri, where pulmonary edema may occur, an early weakening of the left ventricle with hypertrophy of the right ventricle may be observed. Under these conditions the lungs are not pale, as assumed by Sahli, but on the contrary congested. This edema is therefore again obstructive in character. In addition there may be a constriction of the pulmonary and bronchial arteries which leads to a regurgitation of the blood into the lung capillaries. Similarly this author interprets the terminal pulmonary edema generally as obstructive and mechanical in character. Therefore in the agonal edema red corpuscles are usually mixed with the transudate.

This interpretation of the origin of pulmonary edema is also in agreement with experiments of Modrakowski and Matsuoka, in which they perfused the isolated lungs, or Starling's lung and heart preparation, and found that the occurrence of edema depends upon such a relation between the pressure in the inflowing and outflowing fluid that an increased capillary pressure and congestion of fluid in the capillaries result. We may conclude that the mechanical factors which lead to edema of the lung cause a capillary congestion of the lung. An actual paralysis or impairment of the left ventricle may not be necessary for this purpose; a very efficient working right ventricle may be able to produce an edema of the lung, notwithstanding the continued pumping of the left ventricle, especially if the latter works against increased resistance.

However, while the best evidence favors the conclusion that passive congestion in the lung may lead to pulmonary edema, it seems that, on the whole, the lung tissue is relatively resistant to those effects of obstruction and that in many cases circulatory deficiencies are not followed by edema. In certain cases of pulmonary edema no signs of passive congestion are noticeable according to Sahli.

In many cases of chronic cardiac decompensation, with passive congestion of the lung, pulmonary edema does not occur. Either the back-pressure of the blood must be very great or the tissues must be relatively little resistant, before edema results. Such a low degree of tissue resistance plays apparently a certain rôle in pulmonary

edema in the rabbit. On the other hand it is possible that secondary tissue changes, which occur in the course of passive congestion in the lung, may in certain cases prevent edema, yet it may very well be that even in passive congestion, if edema should occur, it is not so much the mechanical factor of increased back-pressure of the blood which is responsible for this result as the change in the tissue of the lung. Thus Lubarsch suggests changes caused by bacterial infection as a cause of pulmonary edema. Modrakowski likewise states that in diseased lungs, edema occurs more readily than in normal lungs, and that ammonia mixed with the circulating fluid causes edema independently of mechanical factors. Fleisher, Hoyt and Loeb observed that a solution of calcium chloride, approximately isotonic with a 0.85 per cent solution of sodium chloride, added in the proportion of one volume of calcium chloride to five volumes of sodium chloride solution, almost doubles the frequence of pulmonary edema, and Carrion and Hallion and others found that hypertonic sodium chloride solutions, injected intravenously, are more liable to cause edema in the lung and elsewhere than isotonic solutions. Roger and Garnier produced edema of the lung in rabbits in which they injected intravenously sodium chloride solution to which gum or gelatin had been added. In this case the pulmonary edema was presumably due to the increase in the quantity and viscosity of fluid circulating in the vessels; there was neither a rise in the blood pressure nor an impairment of the left as compared with the right ventricle under these conditions. Klemensiewicz states that old serum, used in perfusing lungs, more readily causes pulmonary edema than fresh serum. However, the most convincing example of edema of the lung due to the alteration of the lung tissue is that caused by inhalation of poisonous gases like chlorine and phosgen. Though E. Schaefer, and following him Weller, assume that even in this case mechanical factors play a considerable rôle, the chlorine changing the viscosity of the blood and leading to stasis and thrombosis in the lung and elsewhere. L. Hill as well as Laqueur and Magnus have shown that these gases cause edema of the lung primarily by altering the tissue, increasing the permeability of the vessels and injuring the endothelial lining of the alveoli. Hill especially has proven that chlorine gas may cause edema in concentrations which do not yet alter the blood in such a way that stasis occurs.

We find thus good evidence for assuming that changes in the permeability of the pulmonary capillaries and concomitant alteration of the alveolar epithelium may lead to pulmonary edema, but we may go even further and consider whether the edema caused through mechanical obstruction in the circulation is not likewise in certain cases due to an increase in the permeability of the capillaries. Reasons similar to those which apply to general edema in cardiac decompensation, make it probable that this factor is also of importance in pulmonary edema.

Considerations of a like nature apply furthermore in all probability to the pulmonary edema observed by F. Kraus in cats, in which a double vagotomy had been carried out; here intravenous injection of a normal salt solution caused edema, while in normal animals the salt solution was without effect; however, the manner in which the cutting of the vagus alters the tissue in this case is uncertain.

If we summarize these observations, we may conclude that in all probability edema of the lung is produced through an increase in the permeability of the capillaries, which is the result of their dilatation. This dilatation may be brought about through mechancial obstruction within the circulation, or it may be brought about through the action of irritating substances and the edema may, in this latter case, be increased through the destructive effect of these substances on the tissues.

If the increased permeability is produced through mechanical interference with the circulation, blood pressure effects may be added to the changes in the permeability of the vessels and may thus increase the edema. In certain cases when the mechanical obstruction is very intense and especially if the tissue possesses normally a small degree of resistance, the pressure itself may suffice to cause edema of the lung.

Pulmonary edema is also of interest in another respect; it clearly demonstrates that we have to deal in edema with a pressing out of fluid from the vessels rather than with an attraction of fluid by the colloids of the tissues surrounding the vessels, and, as Hill observed, large amounts of fluid can be found in the interstices around the blood vessels.

We may assume that as in other kinds of edema, so also in pulmonary edema, we have to deal with changes which lead to a pressing out of the fluid from the blood-vessels into the lung tissue proper and which at the same time render more difficult the movement of fluid in the opposite direction. Whenever these changes are lacking an abnormal distribution of fluid is corrected apparently without much difficulty, as for instance, in the experiments of Winternitz who found that fluid injected intratracheally into the lungs of dogs is soon absorbed and that such an injection does not lead to a real pulmonary edema.

As to the treatment of pulmonary edema, Haven Emerson found that artificial respiration can save the life of cats in which, following injection of large doses of adrenalin, pulmonary edema is beginning to develop. This author believes that the artificial respiration causes a flow of blood to the left ventricle and prevents its stagnation in the lungs. L. Hill likewise observed the beneficial effect of artificial respiration in pulmonary edema caused by chlorine gas. He attributes it however to the pressing out of fluid from the alveoli.

Laqueur and Magnus found that in cats double vagotomy prevents or at least decreases the intensity of edema of the lung which develops after inhalation of phosgen gas. They believe this effect to be due to the interference with the transmission of sensory stimuli from the lung caused by this process. This observation would therefore confirm the importance of sensory stimuli in the development of inflammatory edema. These authors furthermore succeeded in lowering the mortality from phosgen gas poisoning through the subcutaneous injection of calcium salts previous to the development of pulmonary edema. Thus in a certain number of cases the intensity of the edema was diminished and the mortality fell from 88 to 55 per cent. In agreement with Chiari and Januschke they assume that calcium changes the texture of the tissue in such a way that the walls of the lungs become less permeable to fluid. It may, however, be possible that the effect of this treatment is due to a contraction of the pulmonary vessels and that calcium chloride thus decreases the permeability of the latter. On the other hand, Boycott, who had carried out similar experiments on the action of calcium salts on the escape of fluid from the pulmonary vessels following the use of poison gas in goats, did not obtain beneficial results, or at least the effects of this

mode of treatment were not striking. As we have stated above, addition of a sufficient amount of calcium chloride to a solution of sodium chloride increases rather than diminishes the incidence of edema of the lung after intravenous injection of this fluid. Under these conditions calcium chloride evidently does not lead to a constriction of the vessels nor to a decrease in the permeability of the tissues.

A more marked effect in the prevention of pulmonary edema can be obtained in rabbits through intravenous injection of a considerable quantity of a 25 per cent solution of glucose, soon after the application of the phosgen gas. Hypertonic solutions of sodium chloride on the other hand do not have this influence in the rabbit and in the cat they may even increase the pulmonary edema, in accordance with the observations cited above. While thus prevention of edema is possible in rabbits, in cats even a 25 per cent solution of glucose is without effect. We may assume that in the case of rabbits the positive results are due to osmosis, water being withdrawn from the walls of the blood-vessels and tissues which are thus made less permeable to the plasma; in addition a withdrawal of fluid from the interstices and alveoli of the lung tissue may possibly occur. In contrast to these positive results, Erlanger and Gasser did not obtain noticeable results from the injection of hypertonic gum acacia solution in edema of the lung caused by inhalation of poisonous gas. They attribute this failure to changes in the capillaries caused by the gas, which lead to an increased permeability of the vessels. If the vessels act like a sieve an increase in the osmotic pressure inside the vessels can be of little avail.

VIIa. ON A MECHANICAL FACTOR IN THE DEVELOPMENT OF EDEMA IN THE PLEURAL CAVITY

In the course of pneumonia due to hemolytic streptococci, pleural exudate may develop very rapidly. Through experiments performed in vitro with excised lung, in which broncho-pneumonia or edema was present previous to excision, Graham found that at the end of expiration much fluid is squeezed out from the tissue into the pleural cavity, and that consequently without respiratory movements the amount of inflammatory pleural exudate remains much smaller. Mechani-

cal factors of a similar kind may also influence the amount of edematous fluid in diseased individuals under certain conditions; fluid may perhaps be squeezed either into the pleural cavity or into the lung vesicles; and it is thus also conceivable that the movements of the diaphragm and of the intestines may increase the ascitic fluid in some cases.

VIII. EDEMA OF THE BRAIN

Edema of the brain is, in the majority of cases, due either to circulatory disturbances or to inflammatory alterations of the blood-vessels and tissues. In principle it does not differ from circulatory or inflammatory edema elsewhere, as far as its development is concerned. It owes certain peculiarities to the anatomic relation between subarachnoid space, ventricles of the brain, and the lymph vessels, which show a characteristic arrangement, and also to the fact that the brain is enclosed in a resistant bony capsule; furthermore the soft consistence of the nerve tissue proper is of importance in this connection. As far as we are aware no important additions to our knowledge as to the origin of edema of the brain have been made in recent years. On the other hand some interesting recent contributions indicate that it is possible to modify the intensity of the pressure exerted by the cerebrospinal and interstitial fluid in the brain and thus possibly to prevent or at least to diminish edema of the brain in certain cases.

The investigations of Weed and McKibben have shown that it is possible to influence the volume of the brain and the pressure exerted by the cerebrospinal fluid through intravenous injections of hypertonic salt solutions or distilled water. The former diminishes the brain volume and the pressure of the cerebrospinal fluid, while the latter increases both. Hypertonic solutions of glucose are apparently less effective in this respect. According to Foley and Putnam the same results can be produced through administration of hypertonic salt solutions or of water by mouth or rectum. The changes thus produced may last as long as twelve hours or somewhat longer following the injection; but a return to the normal condition occurs before the end of the second day.

Sachs and Malone undertook the application of these procedures to the treatment of pathological conditions of the brain, caused through

an excess pressure, such as is found in brain tumor or in edema of the brain. Experimentally they succeeded through injection of hypertonic salt solution in dogs in reducing the pressure in the skull which had been raised by experimental means; similar effects were obtained in some patients suffering from abnormal pressure.

Weed and McKibben examined microscopically the brain of cats in which they had produced experimentally changes in the water content. It seems that the changes in the osmotic pressure of the blood affect the behavior of the fluid both in the intercellular spaces surrounding the cells, as well as in the cells proper, causing these latter either to shrink or to expand.

These results agree with the effects of hypertonic solutions obtained by Ellinger in the prevention of pulmonary edema and with the observation of Gayda, who likewise varied the extent of general edema by osmotic factors. We see thus a close parallelism between the experimental procedures used for the prevention or diminution of pulmonary edema and those used for similar purposes in edema of the brain and in both cases the procedures seem to be effective within certain limits.

IX. EDEMA, DUE TO FAULTY DIET

There appeared during the war in various countries, especially of Central Europe, many cases of extensive edema which were due neither to kidney nor to heart diesase. Sometimes they occurred in an apparently endemic form and were associated with dysentery. At first some authors believed that they were of an infectious nature, but soon it was found that they were caused by a defective, insufficient diet. The dysenteric symptoms were usually secondary, probably due to an accompanying edema of the intestinal mucosa with subsequent ulceration. These patients usually had bradycardia and low blood pressure. Cold weather and work aggravated the condition, while rest in bed often led to a discharge of the edematous fluid and recovery, especially when fat or protein was added to the diet. Addition of yeast, vegetables, or fresh eggs did not have a particularly beneficial effect; there was therefore no indication of a deficiency in vitamins.

Investigators differ as to the factor which is mainly responsible for this condition, whether it is lack of protein, lack of fat, or a deficiency of calories. Perhaps all three factors may play a certain rôle, but probably a deficiency in protein is the most important. It seems that the diet of these patients had not only been lacking in important food constituents, but usually it contained an excess of fluid and salt. The latter substances tend to be retained by a poorly nourished body and thus edema may result.

During the period of edema there is some retention of sodium chloride, but usually the latter is present in the blood only in amounts which are normal, or at most approach the upper limit of the amount found in normal persons; however, there may be a slight increase. When the edema is discharged, the urine becomes very rich in sodium chloride, and at that time the sodium chloride in the blood may be found normal or may have become even subnormal. In the main therefore this salt has been stored in the tissues. A diet poor in sodium chloride may accelerate the discharge of the edema. Administration of sodium bicarbonate leads to a retention of sodium in the form of the chloride and thus may favor the development of edema.

The blood is poor in proteins and lipoids; it is hydremic and often hypoglycemic. The number of erythrocytes may or may not be diminished. There is usually an increase in the non-protein nitrogen, especially in the urea fraction in the blood. The molecular concentration of blood and edema fluid seems to be normal, but the sodium chloride content of the edema fluid has been stated to be greater than that of the blood. It is however possible that we again have merely to deal with an unequal distribution of Cl and Na ions in the blood and edematous fluid respectively, similar to that found by R. Loeb, Atchley and Palmer in other kinds of edema. There may be a slight increase of phosphates in the blood. The edematous fluid is relatively poor in proteins. In the urine an increase in ammonia and a great increase in acetone bodies have been found, a condition which points to the presence of an acidosis.

According to Hülse sodium retention produces edema in these patients in a quantitative manner, 0.6 to 1 gram of this salt causing the retention of about 100 cc. of water. If the edematous fluid is discharged, the sodium chloride is again given off. Sodium carbonate

and bicarbonate and sodium nitrate likewise increase edema, but sodium salicylate and potassium acetate diminish it. Under usual conditions addition of water to the diet of these patients is excreted quantitatively, but if they first receive a diet poor in water, the latter is retained if given subsequently in excess.

At autopsy the kidney, liver, heart, spleen are found to be small; the heart and liver may show brown atrophy. In the intestines there is sometimes ulceration. The lungs may show edema and bronchopneumonia.

Digitalis and theobromin do not usually affect the edema, while thyroid extract seems in some cases to be beneficial; calcium salts also may cause discharge of the edema. The polyuria in some cases accompanying this disease is not influenced by pituitary extract, which is so effective in the polyuria of diabetes insipidus. Rest in bed, addition of protein to the diet and a general increase of the amount of food usually lead to the elimination of the edema.

Related to war edema are several other varieties of edema found in cases of under nutrition.

1. In beri-beri edema may occur, if much water is absorbed. McCarrison found associated with the edema a great increase in the size of the adrenals and a true hypertrophy of the medulla of these glands with an excess production of adrenalin. Notwithstanding these findings this author is not inclined to attribute the edema in this case to the action of adrenalin.

(2) In infants, who are inadequately nourished with a diet in which carbohydrates predominated unduly, or in infants in whom the nourishment suffers as a result of intestinal disease, edema may occur. There may be under those conditions a retention of phosphates and sodium chloride or sodium bicarbonate. Here also the retention of sodium chloride may be a factor in the development of edema and, in some cases at least, a diet poor in this salt may lead to the elimination of the edematous fluid. Administration of sodium bicarbonate on the other hand may cause or increase the edema. Acidosis seems to occur in these infants. While in some of these cases lesions have been found in the kidney, in others the signs of kidney disease have been absent. In this connection it is of interest that in infants sodium chloride seems to be eliminated through the kidney less

readily than in older children and thus its administration causes the retention of water, in proportion to the sodium chloride retained.

3. It is possible in animals to call forth edematous conditions through insufficient or faulty feeding. Thus Harden and Zilva produced in a monkey an edema through a long continued diet which, while otherwise satisfactory, was deficient in fat and fat soluble vitamin. In rats edema can be produced through a diet deficient in protein. Addition of casein prevents its occurrence while addition of fat does not have this effect (Denton and Kohman).

Experiments in our laboratory showed that in guinea pigs increased peritoneal transudate is found in cases of underfeeding, without reduction in one particular kind of food stuffs (Hoover). Hoover furthermore found that the same loss in weight produced by a more moderate reduction in diet, but with the addition of thyroid tablets, does not usually lead to an increase in peritoneal fluid. Thyroid feeding prevents therefore the accumulation of fluid in the peritoneal cavity in cases of undernourishment.

4. Joslin, Blum, Falta and others have observed that in diabetes mellitus the addition of large quantities of sodium bicarbonate to the usual diet containing sodium chloride may, in undernourished persons, lead to edema, just as the administration of sodium bicarbonate may, in cases of war edema, in nephritis and in weak infants. In these cases of undernourishment associated with diabetes we have evidently to deal with a condition similar to war edema. In persons undernourished as the result of a deficiency in carbohydrate metabolism sodium chloride and sodium bicarbonate are retained and this leadss econdarily to the retention of water. We may assume that in addition the other factors responsible for edema in cases of undernourishment, which we have just discussed, are likewise present in cases of diabetes. It has been maintained that in diabetic patients the edema caused by administration of sodium bicarbonate can be prevented through subsequent ingestion of hydrochloric acid. If this statement should be confirmed, it would indicate that the alkali is responsible for the edema producing effect of sodium bicarbonate in these cases.

5. In old, but normal persons, administration of sodium bicarbonate or sodium chloride may lead to a retention of water and

thus to a gain in weight, while in younger persons these salts are promptly eliminated. In a case of contracted kidney Achard and Ribot found that addition of sodium bicarbonate to the diet led to a partial retention of the sodium ion contained in this salt, and also to a slight retention of the sodium ion of sodium chloride. The sodium chloride content of the blood changed little under this condition and water was not retained under the influence of the bicarbonate. There occurred therefore a dry retention of sodium bicarbonate as well as of sodium chloride in the tissues.

War edema and similar conditions are of great theoretical interest because they are examples of edema without any apparent impairment of the kidney function and without noticeable heart lesions.

As to the interpretation of this edema we may mention the views of Hülse which resemble in certain respects those of M. H. Fischer. Hülse attributes this kind of edema to a weakened heart action, this latter leading to a retention of substances which increase the binding power of water by colloids. He seems to refer such an effect especially to amino acids and he bases this view on his finding that a diet rich in proteins calls forth edema in such patients or at least makes the discharge of the edematous fluid more difficult. This appears contrary to the findings of other investigators who report a favorable effect of the addition of protein. According to Hülse this action of proteins is due to the retention of nitrogenous substances, particularly amino acids; the latter are excreted less perfectly than ammonia. In nephritis, on the other hand, retention of protein does not lead to edema. Hülse locates this edema, as all other edemas, primarily in the cellular organ protoplasm, in contradistinction to the interstitial spaces. We shall discuss the improbability of this latter conclusion in a subsequent chapter. As to the action of amino acids, it is a very improbable assumption that a relatively small retention of these substances could so markedly increase the water binding power of proteins that edema results.

In accordance with Starling's conceptions of lymphformation Epstein explains starvation edema as due to a deficiency in proteins in the blood. Owing to this deficiency the osmotic pressure exerted by the blood is assumed to be lowered and fluid has therefore a tendency to leave the vessels. In a similar way this author explains the edema in nephrosis as due to a diminution in blood protein.

It is most probable that in all these instances we have to deal with an increased transudation of fluid from the blood-vessels which, as the result of undernourishment, have become more permeable to the passage of a fluid rather poor in protein. Water enters the tissues apparently after they have become richer in sodium chloride, as usual the distribution of water following closely upon the distribution of this salt. However, it is possible that not only changes in the vessels and surrounding tissues and in the constitution of the body fluids are responsible for this effect, but in addition the weakened circulation may be a factor that brings about this result. Furthermore the hydremic condition of the blood present in these cases may not only favor changes in the endothelium of vessel wall, but it may also be responsible for a diminished ability of the blood to hold the water within the vessels.

X. EDEMA OF RENAL ORIGIN

A. Edema of nephritis in man

According to Volhard and Fahr we find in parenchymatous nephritis (nephrosis) a diminution in the amount of urine, associated with a retention of water. At the stage preceding the appearance of edema (latent edema, pre-edema), the number of erythrocytes in the blood is according to these authors normal or even increased. There is therefore no dilution of the blood at this stage of the disease; on the contrary, the latter may be somewhat concentrated. In the edematous stage the vessels are assumed to be very permeable; sodium chloride and water enter therefore the tissues and are not available for excretion through the kidney. The elimination of the edematous fluid is preceded by an influx of water and sodium chloride from the tissues into the blood, which thus becomes diluted. This is followed by an increased elimination through the kidney. Under these conditions the percentage of sodium chloride increases in the urine; but inasmuch as the quantity of urine is still small, the absolute amount of this salt excreted remains likewise small. A diet poor in sodium chloride and water favors the discharge of the edema.

These patients lose an enormous amount of protein through the urine, and this causes a hypalbuminosis of the blood, which has

been erroneously interpreted as a true increase in the amount of fluid in the blood. A similar hypalbuminosis occurs in subchronic and chronic nephritis if complicated by nephrosis. The non-protein nitrogen is not increased in this disease. Volhard assumes that under these conditions edema is due to a pathological increase in the permeability of the extrarenal vessels and that this increase in permeability is caused by a toxic substance originating in degenerating kidney epithelium. This kind of edema is therefore mainly the result of extrarenal factors.

Veil, whose studies are of a more recent date, finds the water and sodium chloride concentration of the blood in this disease normal. The main change concerns therefore the communication between tissues and blood, this communication being altered in such a way that water and sodium chloride are drawn from the blood in the direction towards the tissues.

Volhard and Fahr believe that in cases of glomerulonephritis in which edema is prominent, a secondary nephrosis has developed and that the epithelial degeneration of the tubules is the cause of this edema.

No definite relation exists between blood pressure and edema, the tubular change determining, according to Volhard, the edema and the glomerular change the blood pressure.

While in acute glomerulonephritis—which we shall discuss more in detail in the next chapter—most authors find a dilution of the blood, there is, as we stated above, according to Volhard, in diffuse glomerulonephritis, no dilution of the blood, provided it is accompanied by edema. In the glomerulonephritis unaccompanied by edema there may be a dilution of the blood (polyemia). In the latter condition the pathological change concerns principally the kidney and this leads to a retention of water in the blood; in edema, on the contrary, water and sodium chloride are retained in the tissues in consequence of changes in the blood-vessels. In a similar way anuria unaccompanied by edema may be followed by polyemia. In the pre-edematous period on the other hand water is retained in the tissues.

Thus in contradistinction to the views of Widal and other authors, who considered polyemia as a condition leading to edema, Volhard interprets polyemia as a condition which is not usually followed by

edema, but one in which renal insufficiency causes a retention of fluid in the blood. Renal insufficiency furthermore leads often to a retention of non-protein nitrogen, but these substances penetrate into all the tissues and do not therefore cause edema. The views of Volhard have not however been accepted in their entirety by the majority of authors. Thus several investigators failed to find a connection between renal edema and tubular degeneration; furthermore objections were raised by some pathologists to the sharp separation of nephritis proper, an inflammatory condition, and nephrosis, which according to Volhard and others, represents merely a degenerative state of the renal tubules. There may be found not only a hydremic plethora accompanied by retention of sodium chloride in diffuse glomerulonephritis, but according to Reiss edematous patients often have hydremia, while anhydropic patients may show a normal water content of the blood. Veil also finds usually in glomerulonephritis hydremia accompanied by hyperchloremia and the same may even occur in nephrosis (Frey). When the hyperchloremia subsides, a marked excretion of sodium chloride occurs and the hydremic plethora ceases; but hydremic plethora also occurs without hyperchloremia.

More in agreement with the views of Volhard are those of Nonnenbruch, although even according to this author there is no constant relation between renal edema and polyemia (polyemia and hydremia). While in the majority of such cases polyemia is present, if measured by the number of erythrocytes, it is absent in other cases and especially in early cases of edema, particularly nephrotic edema, but also in cases of diffuse glomerulonephritis. On the contrary in this condition the concentration of the blood may be greater than normal.

Nonnenbruch as well as Volhard believes therefore that the origin of the edema in cases of kidney disease may be extrarenal and that it may be caused by changes in the tissues, blood-vessels or in the blood itself. In accordance with this interpretation Nonnenbruch finds that in nephritic patients the drinking of a large amount of water may lead to a greater concentration of the blood even in cases in which the diuresis is inhibited. These observations are interpreted by this author as demonstrating a primary change in the tissues, which draws the fluid from the blood-vessels into the tissues, and this primary tissue change rather than the change in the kidney he

holds responsible for the edema, at least in a certain number of cases. Even in normal persons the drinking of much water may, according to Veil, be followed by an increase in the concentration of the blood, if more fluid is given off through the kidney or into the tissues than is taken in by mouth.

While on the whole these conclusions seem to be justified, we cannot yet quite exclude the possibility that in the condition preceding edema there may have been a very transitory polyemia and hydremia, which stimulated vessels or tissues to such changes that a greater flow of fluid into the tissues followed. This would correspond to the fact that even in normal persons the taking up of much fluid may be followed by a renal secretion which exceeds the intake of fluid and which thus leads to a greater concentration of the blood (Veil). In this case the transitory hydremia or polyemia evidently stimulates the excess kidney excretion. In a similar way in nephritic patients, at the time when they discharge their edema, or when they are ready to do so, an intake of water may lead to an excess elimination of the fluid, although it has been suggested that this reaction is due to a lack of power on the part of the kidneys to concentrate the urine (Haastert).

In chronic glomerulonephritis the excretion of sodium chloride and water can take place in a satisfactory manner and edema may be absent; but at a later stage, if contraction of the kidney progresses, the elimination of this salt occurs with greater difficulty and is always accompanied by a profuse secretion of water. In this chronic stage edema, according to Volhard, is due either to a complication of this disease with tubular degeneration or with cardiac weakness.

According to Veil in cases of anhydropic contracted kidney, movements of sodium chloride take place without the usual accompanying changes in the distribution of water. Thus addition of this salt to the diet does not lead to the usual physiologic plethora, but to the hyperchloremia which is so commonly found in this stage of the disease, even in cases in which a considerable elimination of sodium chloride occurs accompanied by a large amount of fluid.

In a still later stage, when uremic symptoms appear, a hypochloremia occurs which may go hand in hand with a satisfactory diuresis; we may assume that this condition is due to a migration of the sodium

chloride into the tissues and perhaps also into the blood. A similar hypochloremia is also found in cases of poisoning with mercuric chloride and in certain cases of diabetes insipidus, although in the latter condition the mechanism of this hypochloremia may be different. In nephritic hypochloremia the sodium chloride seems to enter the tissue (or blood corpuscles) just as it enters the lungs in the hypochloremia of pneumonia. If in cases of mercuric chloride poisoning the patient recovers, the sodium chloride returns to the blood from the tissues and the blood becomes again normal.

As stated above, in the primary contracted kidney edema is often of cardiac origin. In this condition, in the state preceding the appearance of edema, drinking of much water may be followed by an excessive elimination of fluid. It may be assumed that if this occurs, some occult edema had probably existed previously. If later the heart action becomes sufficiently weak, the elimination of sodium chloride decreases. However, the condition of pre-edema is in these cases usually not so pronounced as in nephrosis. According to Volhard there may be added to the primary contracted kidney a secondary nephritic condition which again may lead to edema. Cystic kidney resembles contracted kidney in that here also polyuria seems to be a frequent symptom. Accordingly in both these conditions edema is usually lacking, although a slight edema may occasionally be observed with cystic kidney.

All the facts mentioned lead to the conclusion that sodium chloride leaves the blood and enters the tissues preceding the appearance of edema, the movement of water following closely upon that of the salt. In accordance with this conclusion are the observations of Leva, who found in patients dying from kidney or heart disease the chlorine contents of the organs to be twice as great, and in the skin even three times as great, as in normal individuals. The water content is not necessarily increased in these cases. But if edema is present, not only the sodium chloride, but also the water content is found markedly increased. There may therefore be a dry retention of sodium chloride and the retention of sodium chloride and that of water do not necessarily take a parallel course in every instance.

If in cases of edema, elimination of the edematous fluid occurs, sodium chloride and water move first from the tissues to the blood

and lead here to a temporary dilution. This is followed by a copious renal excretion of these substances which may cause a temporary inspissation of the blood.

As we stated, it is assumed that plethoric conditions of the blood (polyemia) occur in certain cases. It is believed that in acute glomerulonephritis a hydremic plethora may occur; it is also believed to occur in certain cases of cardiac edema and according to Widal it is found in chronic nephritis preceding or accompanying the edema. Frey observed it in cases of nephrosis. It must, however, be stated that the methods, which have commonly been used in establishing a hydremic plethora, are not above criticism. Thus Widal, assuming that the protein content of the serum is a constant, made use of the refractometric method, and he finds in certain cases a polyemia, when there is reason to believe that there might have existed merely a hypalbuminemia. The determination of the hemoglobin and of the number of erythrocytes in the circulating blood is likewise not quite trustworthy in chronic diseases.

Much more reliable seems to be the method devised by Keith, Rowntree and Geraghty for this purpose. In applying this method, Bock found the blood plasma volume to be normal and constant in cases of chronic nephritis with edema, in cardiac edema and in salt edema in diabetes. The results obtained with different methods thus do not entirely agree and it would be desirable to repeat these determinations, making use of the newer methods.

The factors which cause the tissues or blood-vessels in nephritis to change in such a way that sodium chloride and water are retained in the tissues are not definitely known. The large majority of authors, since Cohnheim and Magnus, assume that toxic substances change the vascular permeability. Volhard, in accordance with a similar hypothesis of Ascoli, suggests that substances which originate in the degenerating tubule cells enter the circulation and thus are responsible for this effect. A certain basis for this view may perhaps be seen in the experiments of Timofiew, who obtained from kidney tissue a lymphagogue substance, which retards the coagulation of the blood and apparently may enter the circulation in animals in which the renal artery or the ureter has been ligated. In such animals an intravenous

injection of sodium chloride solution causes a more extensive edema than in normal animals. Timofiew concludes that such substances constitute an important factor in the development of renal edema; he furthermore assumes that in certain other cases of edema, where renal lesions are absent, similar substances may be given off by other organs. At present these considerations are largely hypothetical. Magnus found that edema follows the intravenous injection of sodium chloride solutions, even in nephrectomized animals, where such substances cannot play any part; so it is doubtful, how far the lymphagogue found by Timofiew is specific for kidney tissue. On the other hand degenerative processes in organs other than the kidney are usually not followed by edema.

M. H. Fischer assumes as the cause of renal edema, as well as of edema generally, the production of acid in the tissues, which would lead to an imbibition of water by the colloids. We shall have occasion to discuss this theory later, and we shall cite facts which make this interpretation very improbable. However, some recent observations of Rohonyi, when taken by themselves, might be assumed to favor Fischer's view. This author found in cases of nephrosis a tendency of the patients to secrete an alkaline urine. According to this author there are indications that this peculiarity is not due to an abnormal excretory activity of the kidney tubules, but to changes in the tissues which lead to an increased movement of Na_2HPO_4 into the blood-vessels, and to an increased retention of the acid phosphates in the tissues. The mechanism of this condition, provided its origin should actually be in the tissues, is at present quite unknown. In a later chapter we shall discuss more fully the possible connection between acidosis and edema.

The edema, or at least the water retention, which may follow the intake of large doses of salicylates and which has been studied by Hanzlik, Scott and Reycraft, may also be due to the injury of the kidney function and may therefore be related to renal edema. The tissues do not seem to be primarily involved and the administration of sodium bicarbonate does not counteract this effect.

There is no indication of a causal relation between blood pressure and nephritic edema. In nephritis we find an increased blood pressure in conditions which tend to be accompanied by a retention of

non-protein nitrogen and in uremia, while in nephrosis (parenchymatous nephritis), in which the edema is very prominent, no marked rise in blood pressure usually occurs. According to Dorner as well as to Miller and Williams, intake of much fluid may cause an increase in blood pressure in chronic nephritis and in arteriosclerotic kidney disease, while in nephrosis Dorner finds that the intake of much water does not lead to a rise in blood pressure. This author interprets this finding as indicating that in those conditions which lead to edema the vessel wall is abnormally permeable and the vessels do not therefore retain the fluid, in contradistinction to the condition found in chronic nephritis, where the blood-vessels do retain it. In acute nephritis the administration of large amounts of water and sodium chloride causes a true plethora and the heart becomes dilated. This may be considered an edema of the blood. A similar dilution of the blood occurs after water intake in cases of onesided nephrectomy.

It is probable that, as the result of renal insufficiency, the movement of water and sodium chloride from blood-vessels to kidney or tissue and from tissue to blood-vessels is interfered with in various ways. Under certain conditions the movement of water and salt in the direction from blood-vessels to interstitial tissue spaces and serous cavities exceeds definitely the movement in the opposite directions. The exact mechanism to which this abnormal movement is due is not known at the present time. However, we may assume that it is initiated by the insufficient secretory activity on the part of the kidney. When it is present in mild intensity it may lend to pre-edema; when it is present in greater intensity it may lead to edema.

B. EDEMA IN ACUTE GLOMERULONEPHRITIS (TRENCH NEPHRITIS)

The frequency with which edema was observed in acute glomerulonephritis during the war provided a rare opportunity to study the water and salt exchange under these conditions. The results obtained by different investigators are, however, at least in certain respects, contradictory, especially as to the state of the blood in this disease. Thus Nonnenbruch states that in the early stages, previous to the formation of the edema, or in the beginning of its formation,

the blood is more concentrated, water and sodium chloride leaving the blood at that period to enter the tissues. He interprets this condition as due to an abnormal permeability of the injured vessels. Other investigators, especially Thannhauser, did not observe this concentration of the blood, but on the contrary found that the blood was diluted and that there was an increase in the percentage of sodium chloride. Widal, Benard and Vaucher also found a dilution of the blood and Nonnenbruch likewise observed this condition in the later stages of the disease.

Nonnenbruch concludes furthermore, in opposition to Volhard, that edema may be present in acute nephritis without tubular lesions, the absence of which is shown by the satisfactory excretion of sodium iodide through the kidneys. If a large amount of water is given by mouth to such patients, it causes neither diuresis nor dilution of the blood, but it is retained in the tissues (Siebeck). While the concentration of sodium chloride in the blood serum is somewhat increased, it is normal or subnormal in the urine. As soon as diuresis sets in sharply, the percentage of sodium chloride in the urine increases and the quantity of sodium chloride excreted becomes relatively greater than the quantity of water; but if the discharge of the edema takes a more protracted course, the concentration of the urine remains normal. The condition of the blood in acute glomerulonephritis is similar to that found in the uranium nephritis of rabbits.

If in cases of acute glomerulonephritis a diet poor in sodium chloride is given, the concentration of this salt in the blood serum does not fall to so low a level as in normal persons. If an excess of sodium chloride is added to the diet, the results vary according to Thannhauser in different cases. The excess may enter the tissues and cause here a rise in concentration of this salt, while in the blood the concentration remains as before. After a few days the sodium chloride concentration of the edematous fluid recedes to its previous level and, if diuresis occurs, the level becomes lower than that of the blood, the salt evidently passing from the tissue into the urine. In other cases the concentration of sodium chloride and the water content of the blood serum increase after the addition of sodium chloride to the diet, while the concentration of this salt in the urine remains subnormal. If the excess of sodium chloride is given in later stages of the

disease, there may still be some slight abnormalities in the distribution of the salt and water. The concentration of sodium chloride in the blood may reach the highest level which occurs in normal persons; at the same time the amount of sodium chloride eliminated through the urine is increased, although the concentration of this salt in the urine is not increased; this is due to the fact that under these circumstances a large quantity of water is secreted by the kidney.

If the excess of sodium chloride is given at the time when a sudden discharge of the edematous fluid occurs, more salt is excreted in the urine than has been added to the diet. Non-protein nitrogen, sugar, uric acid behave similarly to sodium chloride. Thannhauser concludes that insufficiency in renal function is a factor in the development of edema, but that pathological conditions in the capillaries or tissues may also play a part, especially in cases of acute elimination of the edematous fluid, where the mode of elimination resembles that in cases of war edema, in which kidney lesions are absent.

While the diminished excretion of sodium chloride—which exists notwithstanding the high level of this salt in the blood serum—favors the conclusion that the insufficiency of the renal function is at least partly responsible for the edema in this condition, Volhard brings forward some facts which, according to his interpretation, prove that extra-renal factors are primarily the cause of the edema. Thus he finds that in diffuse glomerulonephritis (war nephritis) a diuretic such as euphyllin, causes primarily a movement of water from the tissues to the blood. Similarly a diet restricted as to the amount of water as well as of solid food leads to a movement of fluid from the tissues to the blood. Thus the edema is mobilized preliminary to its elimination through the kidney.

In the state of pre-edema Volhard and Fahr find a retention of water after addition of large quantities of fluid to the diet, and a tendency toward retention of lactose. In this period the tissues take up the water and thus the kidneys do not receive the stimulus that would otherwise lead to the elimination of the edematous fluid. These authors consider the abnormal permeability of the peripheral capillaries as the principal cause of the abnormal movement of fluid and salts towards the tissues. This condition is independent of hydremia and constitutes the pre-edema of Widal. There may under certain con-

ditions exist a hydremia (hydremic plethora, polyemia) which is due to insufficient functioning of the kidney.

According to Volhard the discharge of the edematous fluid is caused by a movement of fluid from the tissues to the blood and kidney rather than by a primary change in the secretory power of the kidney. Various measures may hasten the discharge of the edema; a diet poor in water and salts (Thannhauser), administration of calcium salts or of potassium acetate (Schultz). Purin bodies and intake of much water are usually without effect, as long as the tendency to retention of water exists; but as soon as there is a tendency to eliminate the edematous fluid, pheophyllin or a large amount of water may cause or increase the diuresis (Volhard).

Eppinger in his studies on the effect of thyroid substance on the movement of water and salts found some additional facts which demonstrate the significance of extrarenal factors in the development and discharge of edema. In confirmation of Reichel, he observed that a solution of sodium chloride injected subcutaneously is absorbed much more slowly in cases of nephritis than in normal persons; a solution of this salt given by mouth is eliminated much more promptly than a solution given subcutaneously. Furthermore if blood is withdrawn from the vessels of a nephritic patient the usual flow of water from the tissues to the blood-vessels takes place, but the movement of sodium chloride from the tissues to the vessels is interfered with.

These observations make it necessary to assume that there exists some factor which holds back water and salts in the tissue or prevents their movement from the tissues into the blood-vessels, and that this change is an essential factor in the production of edema in these cases.

M. H. Fischer and M. Hooker assume that in trench nephritis as in all other cases of edema the primary factor is an acidosis in the tissues which leads to a swelling of the parenchyma and intercellular substances. In case such a swelling affects the brain substance, uremia may occur. According to these authors streptococci are responsible for both the kidney lesion and tissue changes. We shall discuss these views in a later chapter.

Summarizing we may then conclude that in acute glomerulonephritis the exchange of fluid and salt at the boundary line of tissue-blood-vessels is altered in such a way that a surplus movement of water and salt takes place in the direction from vessels to tissues. At the same time the movement in the reverse direction is impeded. This condition is primarily caused by the decreased permeability of the kidney tissue and is often accompanied by a damming up of water and salts in the blood-vessels; but it may be present without such a damming up, especially at the period of pre-edema or latent edema. A similar mechanism, leading to altered movement of water and salt at the tissue-blood-vessel boundary, may exist independently of a primary kidney lesion. This mechanism may be influenced by various substances, again without relation to effects of these substances on the kidney activity, and substances or interferences which tend to increase the movement of water and salt at this boundary line in the direction from tissue to blood-vessels may initiate the discharge of the edematous fluid at a time when conditions in the kidney have become more favorable for the increased secretion of sodium chloride and water.

C. Experimental nephritis and edema

Through administration of a variety of toxic substances like arsenic, salts of mercury, cantharidin, chromates and uranium nitrate, an experimental nephritis may be produced in animals. However the number of substances which cause a nephritis associated with edema is much more limited. Thus of all the substances named, uranium nitrate is the only one which regularly causes edema in rabbits, provided this salt is given together with a sufficient amount of water. In a similar manner Dickson produced marked edema in guinea pigs through administration of uranium nitrate, extending over long periods of time.

Arsenic, chromates and even nephrectomy may however, under certain conditions, lead to edema. Thus Magnus observed edema in nephrectomized rabbits or in rabbits to which arsenic had previously been administered, provided an intravenous infusion of a large quantity of a solution of sodium chloride was made. Injection of amylnitrite

may cause edema in chromate rabbits and greatly increases it in uranium rabbits (Richter). In a similar manner the administration of ricin, snake venom, or nephrotoxic serum causes edema in chromate rabbits (Pearce).

It is generally assumed that these substances injure the capillaries and thus cause edema. They are thus supposed to act similarly to the aromatic diamins which are lipolytic and which according to Hess and Mueller after injection produce edema in contradistinction to the aliphatic amins which are non lipolytic and ineffective. It must however be stated that anatomically vascular changes cannot be demonstrated in animals subjected to the influence of these substances except in some cases in the glomeruli of rabbits which have been subjected to uranium nitrate poisoning.

Heineke believed he had demonstrated in the blood serum of rabbits affected with a uranium nephritis a substance which, after intravenous injection into chromate rabbits, caused edema. Subsequent investigations made it however very probable that this interpretation was erroneous and that such a substance did not exist. Schlayer and his collaborators made an effort to prove that all substances causing general edema produce a functional change in the blood-vessels in contradistinction to changes in the tubular epithelium, which latter were thought to be without significance in the causation of edema. However, this distinction between the effect of these substances on vascular endothelium and on tubular epithelium cannot be upheld, and McNider especially has shown that uranium nitrate, which is most efficient in causing edema in rabbits, may leave the renal vessels intact not only anatomically but functionally.

As stated above, of all the substances named, uranium nitrate is the most efficient in causing edema. In order to obtain a clue as to the manner in which this substance may produce this effect, it was of interest to study the way in which the exchange of salts, of sodium chloride in particular, and water between the various constituents of the body, differs in normal, nephrectomized and uranium animals. Richter and Schirokauer first observed a dilution of the blood in the later stages of uranium poisoning. Fleisher and Loeb found an increase in the osmotic pressure of the blood in uranium nitrate rabbits; according to Richter and Roth this effect is due to an increase in

nitrogenous substances in the blood. It is likewise present in nephrectomized rabbits and, according to our findings, in animals subjected to other operations as well, even if the latter are not necessarily followed by edema. Similarly the increase in the concentration of sodium chloride in the blood found in cases of uranium poisoning, is observed also in nephrectomized rabbits. The amount of sodium chloride and other osmotically active substances retained in the blood must be even greater than is indicated by the percentage figures, because of the amount of water which is retained at the same time in the blood. In uranium rabbits, tissues as well as blood contain probably an excess of sodium chloride.

Under these conditions it is of importance that we found certain quantitative differences in the action of these factors; these quantitative differences may have some connection with the production of edema. If we inject intraperitoneally into rabbits, a solution of sodium chloride, a dilution of the blood takes place, which is more marked in the later stages of uranium nitrate poisoning than in the earlier stages; only in the earlier stages it is of an intensity similar to that observed in nephrectomized animals. In the earlier stages following uranium nitrate administration there is furthermore an increased diuresis with a slight relative decrease in the elimination of sodium chloride through the urine; but in later stages there is an almost complete anuria. The osmotic pressure of the peritoneal fluid is a little higher after intraperitoneal injection of a solution of sodium chloride in uranium nitrate rabbits than in normal rabbits; but the osmotic pressure is lower in the peritoneal cavity than in the blood in uranium nitrate poisoning, while in normal rabbits the reverse relation obtains: the osmotic pressure being higher in the peritoneal cavity than in the blood. The most characteristic feature which we observed in uranium nitrate poisoning, is however the diminished absorption of fluid from the peritoneal cavity (Fleisher and Loeb), and this exists notwithstanding the rise in osmotic pressure in the blood in this condition. The decrease in absorptive activity is in sharp contrast to the increase in absorption which is noted in nephrectomized animals (Meltzer and Salant, Fleisher and Loeb) and in animals subjected to non-specific operations (Fleisher and Loeb).

In the same way we found a slightly diminished absorption of sodium chloride from the peritoneal cavity. This decrease in the tendency of substances to pass from the peritoneal cavity to the blood cannot be due to the injurious effect of uranium on diuresis, because it is noticeable already at a time when the secretion of urine is increased rather than diminished by uranium. A regulatory mechanism in the distribution of salt and water, which is present in the normal animal, is evidently disturbed in the nephritic animal. These observations conform to the delayed absorption of salt solution injected subcutaneously in cases of nephritis, to which we have already referred in the preceding chapters.

An increased content in proteins in the peritoneal fluid, which we observed in uranium nitrate animals, is likewise present in nephrectomized rabbits, although in the latter the absorption from the peritoneal cavity is accelerated. However, the diminished absorption of fluid from the peritoneal cavity, as well as in the increase in osmotic pressure of the blood, combined with an increase in the protein content of the peritoneal fluid, is found to a still higher degree in cases of peritonitis. The condition characteristic of uranium nitrate animals resembles therefore the changes observed in cases of peritonitis.

Adrenalin increases absorption of a solution of sodium chloride from the peritoneal cavity in the early stages of uranium poisoning; at that period it has therefore an effect similar to that found in normal animals. But it has only a slight effect in later stages of uranium action. In the later stages adrenalin does not diminish the dilution of the blood—an effect, which it has in normal animals after an intraperitoneal injection—but it still increases very slightly the amount of sodium chloride absorbed from the peritoneal cavity.

While caffeine increases absorption of fluid from the peritoneal cavity in nephrectomized animals, it no longer has this effect in the later stages of uranium nephritis; neither does it produce the lowering in the osmotic pressure of the blood in uranium rabbits, which we observed in normal rabbits.

The changed distribution of sodium chloride in uranium nitrate poisoning suggests that also in this condition this substance may be of significance in the origin of edema, but there are some indications

that the intake of water as such may increase edema in these cases. Thus according to Mohr in uranium rabbits in which the sodium chloride content of the tissues has previously been diminished through a diet poor in this salt, the mere administration of water may cause edema. Richter likewise finds that in uranium rabbits large quantities of water may produce edema; nevertheless it seems that the administration of sodium chloride is in such animals much more effective in increasing edema than the mere giving of water.

We see then that uranium poisoning alters to a very marked degree the movements of fluid from the peritoneal cavity to the blood and to a lesser degree also the movements of sodium chloride; it distinctly retards or even inhibits these movements.

The movement of these substances in the opposite direction, namely, from the blood-vessels to the tissues, or the peritoneal cavity has been studied with contrary results by different investigators. While Schmid and Schlayer found an increased rapidity in elimination of sodium chloride and water from the blood-vessels in the later stages of uranium nitrate poisoning, Boycott and Chisholm, Schwarz and Pollak on the contrary observed a definite retardation in the elimination of various substances (salts, water, lactose and sodium iodide). The experiments of Boycott in particular were repeated by Bogert, Underhill and Mendel with similar results. These latter authors found moreover that a subcutaneous injection of morphine given to dogs or rabbits one hour preceding the testing of the vascular permeability has the same effect on the permeability as the poison used in causing nephritis (uranium nitrate, sodium tartrate). There is therefore in these experiments no indication of an increased permeability of the vessels; and indeed, if the last named investigators attribute the condition of delayed elimination found in uranium nitrate animals to a change in the permeability of the blood-vessels, we could have to deal only with a diminished instead of an increased vascular permeability. We must however consider the fact that in nephritic rabbits the osmotic pressure and the sodium chloride content of the blood are increased and that this factor may not be without significance in the delay in the movement of substances from the blood-vessels to the tissues.

It is one of the problems that remain to be determined in the analysis of edema, how far osmotic changes and how far changes in permeability are responsible for the interference with the movements of water and of dissolved substances in the nephritic organism, and it is possible that osmotic changes may be secondary to changes in the permeability in membranes and that thus in reality both of these factors may be involved.

Boycott and Douglas as well as Lewa found in uranium rabbits an increased retention of water and sodium chloride in the tissues (muscle, skin, kidney) and, as we mentioned above, addition of sodium chloride to the food of rabbits poisoned with uranium nitrate leads to an increase in the edema (Heineke). We may assume that this substance finds its way into the tissues and thus increases edema.

Chisholm was able to extract from the kidney of uranium rabbits a non-coagulable substance which when injected intravenously, causes a delay in the elimination of substances from the blood-vessels.

Whether the changes which we described are entirely characteristic of uranium nitrate nephritis which is accompanied by edema, and whether they are absent in animals to which substances have been administered which merely produce nephritis but do not usually produce edema, is not yet completely known and needs some further investigation. While according to Chisholm chromate seems to produce the same vascular and tissue changes as uranium, we do not at present know how the exchange of substances between peritoneum and blood-vessels is affected by the action of chromate. However, an observation of Heineke may be of interest in this connection. He noticed that if through administration of chromate a mild nephritis is produced in rabbits, an excess of sodium chloride and water, given by mouth, leads to a retention of the salt and consequently the concentration of sodium chloride rises in the blood and in the tissues, in contradistinction to normal animals, in which under similar conditions an excess of the salt and water in the food is almost completely eliminated. Yet notwithstanding this retention of sodium chloride, edema is usually not observed in the chromate rabbit and the excretion of water takes place effectively following these changes in the composition of blood and tissues, which are thus evidently of a more temporary character than in uranium poisoning. We have presum-

ably to deal with quantitative differences in the action of chromate and uranium, the former substance tending even toward the production of edema, which is however realized only under special conditions. We see then that the effects of uranium nitrate are as follows: (1) An increased dilution of the blood and an increased osmotic pressure and content of sodium chloride of the blood. (2) An increased retention of sodium chloride and water in the tissues. (3) A delayed absorption of water and sodium chloride from the peritoneal cavity. (4) A delayed elimination of water and salts and other substances from the blood. (5) An increased content of colloids in the peritoneal cavity, and (6) a decreased diuresis and, in later stages, changes in the tubules of the kidney which abolish diuresis completely; however, this diminution in diuresis cannot be altogether the direct cause of the first named changes, because the latter may to some extent be present already at a time when the diuresis is still very good. (7) Adrenalin and caffeine have lost their typical accelerating influence on the movement of salt and water in the body in uranium animals. (8) Administration of an excess of water and especially of sodium chloride increases the edema under the same conditions. In contradistinction to uranium, chromate as such does not cause edema, but may lead to edema, if given in combination with certain other substances, especially substances which tend to change the permeability of vessels, while certain substances, which presumably alter the vessels like cyclic amins, may as such produce edema.

Provisionally we may assume that osmotic changes in combination with an increased content in proteins in the peritòneum, and perhaps in the tissue spaces, and alteration of membranes separating the various organs are responsible for this edema; however, further investigations are necessary for a satisfactory analysis of this problem. It is possible that in addition to the factors we mentioned, still another factor is at work in uranium nephritis. Recent experiments of Morawitz suggest such a possibility. This author inserted small plates of agar into the subcutaneous tissue of animals and by weighing determined the amount of fluid taken up by the agar in a given time. Under conditions which tend toward the production of edema, for instance, after administration of uranium nitrate, the agar takes up fluid, while under normal conditions on the contrary it loses somewhat

in weight. Morawitz eliminates changes in hydrogen ion concentration and in osmotic pressure of the surrounding fluid as the causes of this phenomenon. There remains thus the assumption that in uranium rabbits substances are present in the tissue spaces which tend to increase the water binding power of the colloids in the subcutaneous tissue and probably also in the serous cavities. This conclusion agrees with the finding of Fleisher and Loeb who observed that uranium nitrate rabbits show, as far as the behavior of the fluid injected intraperitoneally is concerned, some similarity with animals in which a peritoneal inflammation exists. In both conditions the intraperitoneal fluid is retained; this effect may be connected with the increase in the amount of colloid in the peritoneal cavity which we found in uranium nitrate animals. In addition there may be present a substance of unknown character which increases the water retaining power of these colloids. However, further investigations are necessary for a more complete analysis of the edema in uranium poisoning.

D. The effect of nephrectomy and other operations on the distribution of water and salts in the body and on the formation of edema

In the three preceding chapters we analyzed the factors which lead to the development of edema, if as the result of deficient kidney function the elimination of water and sodium chloride is inhibited. A pathological change in the kidney might affect the distribution of water and salts in the body and in various ways: (1) The insufficient elimination of water and dissolved substances through the kidney as such might give rise to those secondary alterations in the organism which lead to edema; (2) The changes in the kidney tissue might in some way be responsible for those abnormalities in the movement of water and dissolved substances which result in edema, perhaps by leading to the production of a toxic substance which affects the vessel-tissue boundary layer, or (3) a primary factor may cause defects in the kidney as well as affect the distribution of substances in the body and change the mechanisms which determine the movements of substances through membranes. A comparison of the effects of nephritis with those following extirpation of the kidney may perhaps help in deciding among these various possibilities.

Magnus and other investigators found that, while intravenous injection of a solution of sodium chloride isotonic with blood, does not in normal rabbits lead to general edema, but merely to ascites, it may cause general edema in rabbits which have been previously nephrectomized. In these experiments at least a period of several hours elapsed between the nephrectomy and the intravenous infusion of the sodium. In the experiments of Fleisher, Hoyt and Loeb, on the other hand, the infusion followed the operation immediately. In the latter experiments the amount of ascites was increased in nephrectomized animals to a larger extent than could be accounted for by the amount of fluid in normal animals eliminated through the urine; neither could a change in the rate of infusion alter this result. But after nephrectomy the osmotic pressure of the blood is raised (V. Koranyi, Meltzer and Salant, Fleisher and Loeb). Several authors found the blood more diluted and, at the same time, richer in sodium chloride in nephrectomized as compared with normal animals (Schmid and Schlayer, Roger and Garnier, Brandenstein and Chayes). However, in our experiments, in which very large quantities of fluid were injected intravenously, the dilution of the blood was the same in the nephrectomized and non-nephrectomized animals. This difference in the results obtained may, partly at least, depend on the time at which the nephrectomized rabbits were examined.

In agreement with other investigators Fleisher and Loeb found in nephrectomized rabbits the osmotic pressure of the blood serum, as well as its sodium chloride concentration, increased. Like Meltzer and Salant, Achard and Gaillard they furthermore observed an increase in absorption from the peritoneal cavity in nephrectomized animals. We attributed this increased absorption to the increase in osmotic pressure of the blood, which causes the water to move out of the peritoneal cavity into the blood-vessels.

According to Fleisher and Loeb nephrectomy has the following additional effects: It not only increases the absorption of water from the peritoneal cavity, but also that of sodium chloride. Other osmotically active substances pass instead into the peritoneal fluid. As the result of the intraperitoneal injection of an isotonic solution of sodium chloride, the blood becomes therefore more diluted in nephrectomized than in normal animals, while in the peritoneal fluid on the

other hand the protein content is greater than in normal rabbits, as the result of the increased absorption of water. The sodium chloride which is absorbed from the peritoneal cavity in nephrectomized animals is to a great extent passed on to the tissues. As in normal animals, so also in nephrectomized animals, adrenalin causes an increased elimination of sodium chloride and fluid from the blood and the dilution of the blood is therefore decreased under the influence of adrenalin. But, on the other hand, the absorption of peritoneal fluid is not increased by adrenalin in nephrectomized animals, evidently because in such animals adrenalin does not cause the same additional increase in osmotic pressure of the blood which it causes in normal animals. In nephrectomized rabbits caffeine increases the osmotic pressure of the blood and consequently also the absorption of peritoneal fluid, to a marked degree; it likewise increases the absorption of sodium chloride from the peritoneal cavity and the elimination of these substances into the tissues. It also causes an elimination of water from the blood-vessels into the tissues. In nephrectomized animals caffeine accelerates therefore the reversed current of water and sodium chloride from the blood-vessels to tissues, while in normal animals it accelerates the current of these substances from vessels to kidney. Our observations prove thus definite changes in the distribution of water and salt as a result of nephrectomy, and these changes in the movement of water are at least partly secondary to changes in osmotic pressure following nephrectomy.

With these results on the effect of nephrectomy on the distribution of substances in the organism, agree the findings of Nonnenbruch, who observed on the day following nephrectomy a diminution in the number of erythrocytes in the blood as a result of the movement of water and sodium chloride from the tissues into the blood. In addition a certain amount of protein enters the blood according to this author. Thus a true hydremic plethora is produced. The increase in sodium chloride and protein in the blood may amount to as much as one hundred per cent.

As far as these various changes in the movement of salts and water had already been observed by previous investigators, they had been supposed to be specific effects of the lack of the kidney function and of the subsequent retention of substances which normally are elimi-

nated through the kidneys. According to Fleisher and Loeb, however, some of the effects of nephrectomy do not specifically depend on an interference with the function of the kidney, but are due to the effect of the operation as such. This applies for instance to the increase in the osmotic pressure of the blood and to the amount of fluid absorbed from the peritoneal cavity. Indifferent operations on organs other than the kidney have the same effect in this respect as nephrectomy. Caffeine also causes an increased absorption from the peritoneal cavity in animals subjected to a non-specific operation, as it does in animals which have been nephrectomized. The current views as to any specificity in the effects of the elimination of the kidney function on the distribution of water and salt in the organism must therefore be considerably modified as the results of these experiments. Every operation as such—but not the anesthesia accompanying the operation—has a far going influence on the exchange of substances between blood and tissues.

We have apparently in this case to deal with a reaction of general significance. Thus accompanying the tuberculin reaction a dilution of the serum is said to occur and, according to Friedemann and Fraenkel, during serum disease a retention of water and sodium chloride can be found. It seems probable that here likewise an increased absorption of fluid from the peritoneal cavity and a dilution of the blood would occur, but data in this respect are as yet not available.

It still remains to be determined whether the effects following nephrectomy are quantitatively stronger and of longer duration than those following an operation elsewhere. This may perhaps be expected to be the case.

In certain respects comparable to the results of nephrectomy, seems to be the effect which may follow obstruction in the outflow of urine, for instance, in cases of prostatic hypertrophy. It has been stated that edema may develop under such conditions.

In general we may conclude that some of the effects observed in nephritis are found after nephrectomy and even nonspecific operations, and that some of the factors leading to edema are already present under these latter conditions. Yet we do not actually observe edema in nephrectonized animals. It may be that the difference between the effects of nephrectomy and of uranium nephritis is merely of a quan-

titative character, or it may be that in nephritis, toxic substances play a rôle, and that these are lacking after nephrectomy.

However that may be, the experiments mentioned in this chapter are of interest because they so very clearly demonstrate the great significance in osmotic and diffusion potentials in the movements of water through membranes within the organism. Furthermore they demonstrate the fargoing influence of operations in general and of various other interferences, not affecting the kidney, on osmotic changes and on movements of substances in the organism.

XI. THE SIGNIFICANCE OF SALTS IN EDEMA

A. The distribution and movements of water, sodium chloride and non-protein nitrogen in the body

In the preceding chapters we have repeatedly found instances of a relation between the distribution and movements of salts, particularly sodium chloride, and of water, and also a relation between the movements of salts and the development of edema. It might therefore be advantageous for the analysis of edema to review some of the more important factors in the distribution of water and salts as contrasted with non-protein nitrogen in the body. It was the problem of edema which led to a more searching study of the movement and distribution of salts and water in the normal organism. Magnus showed that after an intravenous injection of a hypertonic solution, this salt passes first from the blood into the tissues and subsequently from the tissues back into the blood and into the kidney. Following the injection the tissue gives off water to the blood, but this is not sufficient for the rapid elimination of the injected salt through the kidney and temporarily therefore the salt is stored in the tissues. Engels found that the muscles represent the main depot for water in the normal organism, especially after an intravenous injection of a diluted solution of sodium chloride. Next to muscle, the skin takes up a relatively large amount of water, although much less than muscle. Overton made it probable that a part of the fluid taken up by the muscle is stored in the interstices between the muscle fibers proper. According to A. Mayer and Schaeffer a great constancy exists in the water content of different organs; the content differs however in different species.

The percentage of sodium chloride in kidney, lung and intestines is considerable; the absolute amount of this salt is greater in musculature and skeleton but the main depot for its storage is the skin. If much sodium chloride is taken up, it is stored chiefly in the skin from which it is again given off in larger quantities than from other places in case of sodium chloride deficiency (Wahlgren and Padberg). Those organs whose function it is to eliminate it seem therefore to be the principal depots for this substance, and a connection seems to exist between the secretory function of the organ and its function as a storing place for the substance to be secreted. However, the exact point where this salt is deposited in these organs remains, as far a we know, still to be determined.

It is of interest to compare with the behavior of sodium chloride the distribution of some of the organic nitrogenous constituents of non-protein character.

In contradistinction to inorganic salts, amino acids are carried to all the organs after they have entered the blood from the intestinal canal (D. Van Slyke and Meyer). According to Schoendorff, as well as to Marshall and Davis, urea is distributed approximately equally among all organs and the blood. Recent investigations of Becker on the other hand make it seem probable that the total non-protein nitrogen may be unequally distributed in the body, and the finding of Klein, as to the distribution of non-protein nitrogen in heart and kidney diseases, agrees with the latter conclusions.

Wherever water occurs in the body, there are present at the same time colloids, particularly proteins, and crystalloids, among which salts are prominent. Water enters into relation with both of these substances and the proteins especially have a great importance in binding the water. However the effect of the proteins on the water varies in accordance with the state of these colloidal substances. Here we shall refer only to certain aspects of this question, leaving the discussion of the problems in detail as to the relation between water and colloids to a subsequent chapter.

Woodyatt distinguishes between free water and bound water, the latter being in combination with colloids and crystalloids. Only the free water is available for immediate use, the bound water representing a reserve. According to Woodyatt free and bound water

are in an equilibrium. If through an increase of crystalloids or colloids the bound water increases at the expense of the free water, available for elimination, fever is produced. Important as it would be to determine the availability of water for different functions, and the amounts available in each case, there seem to be some difficulties in the classification of Woodyatt. The water bound electrostatically to colloids and diffusible electrolytes and the water which is merely under the influence of osmotic forces in the solution are not well defined at the present time. The latter would essentially represent the free water. According to Woodyatt it would be especially the water of so-called imbibition which would have to be considered as bound water. Now according to Jacques Loeb, osmotic forces are an important factor even in determining the imbibition of protein gels or micellae.

From a practical point of view, it might be preferable to distinguish between, (*a*) the water in the circulating body fluids (lymph and blood); it is especially the circulating water of the body which is available for excretion (Adolph); (*b*) the water in the loose tissue spaces (*c*) the water in the parenchyma of organs generally, (*d*) the water in the special storage places which serve as reservoirs.

We have seen that the distribution of sodium chloride and of water in the body are not identical, especially as far as the storage places are concerned; yet to a great extent their retention and elimination take place in the same direction and manifest a mutual dependence even in the normal organism. This is shown by a series of recent investigations. On a diet poor in sodium chloride, a healthy person loses weight by giving off an excess in water. On the contrary in undernourished persons water and sodium chloride are not excreted in the same ratio as in normal individuals, but retained. According to Veil, after feeding a diet poor in sodium chloride, an increased concentration of the blood is found at a certain point; this is accompanied by a loss of weight and a negative sodium chloride balance. The sequence of events in this case seems to be as follows: In the first twenty-four hours an excess of sodium chloride is excreted through the kidney and sodium chloride moves from the tissues and perhaps also from blood cells to the blood plasma. Still the sodium chloride percentage of the blood is diminished; notwithstanding this diminu-

tion, more salt passes into the urine than is accounted for by the loss in the blood. It must therefore have come from the tissues or cellular elements of the blood. On the second day the blood loses water and becomes more concentrated, an increase in concentration which is similar to that which may occur in complete starvation. If sodium chloride is now added to the food, both the sodium chloride percentage of the blood and its water content increase again. If an excess of sodium chloride is given with the food, an increase of this salt and of water occurs in the blood on the first day, leading to a temporary serous plethora; on the second day both sodium chloride and water pass from the blood into the tissues and on the third day they return to the urine and are secreted.

According to Thannhauser in healthy persons the retention of sodium chloride and water in the blood, after addition of sodium chloride to the diet, is only very slight and less than could be expected from Veil's statements. The results of Veil agree with those obtained by Haldane and Priestly. According to these investigators the intake of water by mouth does not result in a noticeable dilution of the blood, but following the ingestion of the same quantity of an isotonic salt solution a dilution occurs. The increase in concentration of the blood under the influence of a diet poor in sodium chloride to which we referred above, and the significance of this salt for the retention of water, become still more evident under special conditions when for other reasons a loss of water occurs. Thus in the mountains a diet poor in sodium chloride may cause an increase in the hemoglobin of the blood. Similarly perspiration in a person with a deficit of sodium chloride in the diet leads to a concentration of the blood. The deficit in sodium chloride evidently prevents an efficient movement of water from the muscles and other tissues to the blood. A similar concentration of the blood may follow perspiration under conditions which lead to a rise in temperature. It is different under normal conditions; here, on the contrary, increased perspiration induces movement of water from the muscles to the blood, which may more than compensate for the water lost through the skin and may lead even to a temporary dilution of the blood (Cohnheim, Table, Gross u. Kestner, Cohn, Plant u. Wilbrand). The importance of sodium chloride for the economy of water in the organism is also

evident if water is lost through diuresis. A diet deficient in sodium chloride delays or prevents the body from making good the loss of water caused through caffeine diuresis; and correspondingly caffeine causes a greater diuresis in an organism which has previously been made deficient in sodium chloride (Bogendörfer).

Drinking of water may cause diuresis, if the organism has previously received a sufficient amount of water; but after a preceding diet rich in sodium chloride and relatively poor in water, it does not cause diuresis (Siebeck). The diuresis may lead to the elimination of an amount of water which is greater than the excess of water ingested, which induced the diuresis. The amount of the water and salt, ingested in the period preceding the observation, determines the mode of reaction to a new water intake, not only in normal persons, but also in patients suffering from kidney disease, and in particular does the amount of water administered in the period preceding the test determine the capability to eliminate water given in excess. We must assume that under these conditions salt and water which are stored in the body are not retained in the blood, but in the tissues. Thus Veil found in a young diabetic a retention of sodium chloride in the tissues which was accompanied by a lowered amount of sodium chloride in the blood; in a similar way, water taken in excess, does not necessarily lead to a dilution of blood, but it may be transported to the tissues. This condition, if it becomes quantitatively stronger, gradually passes into latent edema or pre-edema, which precedes the open appearance of an edematous state under pathological conditions. Conversely if, after an excess intake of water, the water is abundantly eliminated through the kidney, a considerable dilution of the blood may be present owing to the passage of water from the tissues into the blood preliminary to the elimination of the water through the kidney.

We have already mentioned several instances in which a disturbance in the water and sodium chloride equilibrium, at a certain place in the body, leads to an excessive counter move, a reaction which more than balances the disequilibrization caused through the primary disturbance and which may thus lead to a secondary disequilibrization. Only gradually regulating mechanisms set in and correct again this excessive reaction. An additional example of this condition is the

following: When hypertonic glucose solutions are injected into rabbits (Lipschitz) or man (Bürger and Hagemann), the blood becomes at first diluted as a result of the entrance of tissue fluid into the blood. This fluid is relatively poor in nitrogen and salts and the blood is therefore likewise temporarily poorer in salts and nitrogen. The hydremia however induces diuresis and, as a result of the excess elimination of fluid through the kidney, the blood now becomes more concentrated. This change is accompanied or followed by an increased passage of sodium chloride and water from the tissues to the blood. Therefore a second hydremia occurs, which may be associated with a temporary hyperchloremia, and this is gradually corrected through the activity of the kidney.

Under ordinary circumstances the retention of water which follows the retention of sodium chloride, or certain other substances, is merely a temporary condition, which lasts only until the substance taken up in excess has been eliminated; but if the salts cannot be satisfactorily eliminated through the kidney, they may, as Blum, Aubel and Haüsknecht point out, migrate into the serous cavities and thus cause edema. This agrees with the conception that the serous cavities act as reservoirs in which substances are stored which, under normal conditions, would have been eliminated mainly through the kidney.

While therefore changes in sodium chloride and water concentration in the body go usually hand in hand, they, may, as we have mentioned above, in certain cases be independent of each other. Thus in rabbits poisoned by uranium nitrate and given a diet rich in sodium chloride and poor in water, a dry retention of sodium chloride can occur, especially in the skin (Leva). Even in normal individuals, if the water intake is diminished or the loss of water is increased (for instance, under the influence of the desert climate), a dry retention of sodium chloride may likewise occur (Cohn, Bickel).

Conditions prevailing in certain tissues may lead to an abnormal percentage of sodium chloride in the blood. This occurs, for instance, in pneumonia where the blood becomes relatively poor in sodium chloride, because this substance, as well as water and proteins, show a movement towards the lung. If the crisis occurs, sodium chloride returns again to the blood (Von Hoesslin, Snapper, von Monokow). There is reason for assuming that in pneumonia, as in all foci of inflammation,

the concentration of the hydrogen ions is increased and it has been suggested that possibly as a result of this change the proteins in the exudate become converted into kations and therefore begin to bind the chlorine ions. But there is in the pneumonic exudate, according to Blum, Aubel and Hausknecht, not merely a surplus of chlorine, but also an increase of sodium and for this and other reasons such an interpretation is presumably not correct. However, the increase in osmotic pressure present in inflammatory foci may possibly be partly responsible for the movement of water from the blood and lymph to the lung. The retention of chlorides in pneumonia and certain other febrile diseases was attributed by Snapper to a change in the permeability of the tissue for the chlorine ion. He claimed to have actually demonstrated such an increased permeability in the case of the erythrocytes. However, Siebeck showed that the exchange of the chlorine ions between serum and erythrocytes is identical under normal conditions and in disease. A similar movement of sodium chloride and water seems to occur in cardiac edema of the lung. Here also immediately following the beginning of the edema, the salt and water show a decrease in the blood.

Altered conditions in the tissues are an important factor in other instances also in determining the movemen' of sodium chloride and water. Thus Magnus-Alsleben, Nonnenbruch and Gerhardt found that in certain cases of nephritis, or in heart disease, which is associated with passive congestion of the kidney, the kidney excretes promptly a solution of sodium chloride given intravenously, but holds back fluid or salt given per os. It may however be that in such cases the kidney responds only to the stronger change in concentration following intravenous injection, but is unable to respond to the more gradual change in concentration after oral administration. In normal individuals results seem to be different. In this connection it is of interest to recall the observations of Ginsberg and others, according to which in normal dogs water given by mouth causes diuresis, while intravenous or subcutaneous injections of water do not have this effect.

From all of these studies, as well as from those of Siebeck, Öhme and from the experiments of Eppinger and others, which we shall discuss later, it follows that the condition of the tissues is a deciding

factor in determining how much water and sodium chloride shall be excreted through the kidney, and it follows furthermore that the composition of the blood in itself is not sufficient to explain the changes in the economy of water and salt.

The facts which we have recorded in this and in some previous chapters, and to which we shall add in subsequent chapters, suggest that the movements of salt and water in the body are one connected mechanism, a disturbance at one point of this mechanism leading to correlated and compensatory changes elsewhere. The question remains to be answered how this compensatory regulation takes place. The following observation of Priestly suggests that very slight differences in concentration, if they persist during a sufficiently long period of time, may account for considerable movements of water and salts. After an intake of a large quantity of water by mouth, diuresis follows without being preceded by a noticeable dilution of the blood. However, according to Priestly the electric conductivity of the blood is in such cases slightly decreased and the small decrease in the concentration of salts in the blood may be sufficient to set in motion the regulatory activity of the kidney. The resulting polyuria can be prevented through the subcutaneous administration of extract of the posterior lobe of the pituitary gland.

The drinking of excessive amounts of water is harmless as long as the normal channels of excretion function normally. If by some means this process of excretion is interfered with and the stream of surplus water is turned towards the tissues, serious consequences follow. Thus Larson, Weir and Rowntree observed that if dogs are given 3 cc. pituitary extract and soon afterwards an excess of water, symptoms of poisoning, which indicate very strongly an edematous condition in the cranial cavity, ensue. An excess of water may act similarly in certain animals even without pituitary extract. General edema or an increase in the plasma volume of the blood are however not found in such cases, but there may occur an increased blood pressure and increased intracerebral pressure; administration of hypertonic salt solutions is curative in such cases (Larson, Weir and Rowntree).

In man, similar effects have been observed as the result of an excessive drinking of water, in cases in which by some means the prompt

elimination of the water is prevented. Thus in patients with chronic nephritis and hypertension, the administration of large quantities of water may cause not only an increase in blood pressure (Miller and Williams), but also changes indicating increased intracerebral pressure, and apparently pre-edematous conditions (increase in weight, fullness of abdomen) (Rowntree).

In diabetes insipidus an excessive amount of water is taken by mouth without any symptoms of water poisoning becoming noticeable, such as those observed by Rowntree and others. While there may sometimes exist in this disease a hyperchloremia (Veil), an increase in the volume of blood is not observed (Rowntree); a very diluted solution of sodium chloride moves from the tissues to the blood and from the blood to the kidney and the movement continues even after the excessive drinking of water has been interrupted.

According to Erich Meyer and Meyer-Bisch the changes in the movement of water and salt from the blood to the kidney and from the tissues to the blood are coördinated with each other. Pituitrin causes a reversal of this current; under the influence of this substance water moves from the blood to the tissues and Rowntree found accordingly that, after the administration of pituitrin, the giving of water in the large amounts to which the patient had been accustomed results in marked toxicity, and that even a mild anasarca may develop, in consequence of the excess of water being carried to the tissues.

Disregarding the passage of food substances from the capillaries to the tissues, which occurs generally and continuously, we may assume that a correlation exists between the current of water and dissolved substances, from the blood to the kidney and from the tissues to the blood. The latter current may be reversed under certain conditions. Changes at one point call forth corresponding changes in other parts of the system. Mechanisms apparently exist which correlate these two currents in a definite way as to their intensity and direction. The changes induced tend to be excessive at first and only gradually assume their normal character. In this respect, they resemble reactions to stimuli, and to regenerative processes, where at first the response may likewise be excessive. However, not all of the tissues are equivalent in this respect, but certain tissues form more or less specific reservoirs for certain substances.

The mechanism through which these coördinations occur is imperfectly understood at present, but it seems very probable that osmotic and diffusion potentials and perhaps also electrostatic forces leading to endelectrosmosis together with changes in the permeability of certain membranes, play a prominent part in it and that in particular the movement of sodium chloride is one of the important factors which determines the movement of water.

We may then assume that the currents from the blood to the tissues on the one hand, and to the kidney and other places of elimination on the other hand, balance each other, a current in the one direction detracting from the other. Factors that tend to weaken the current towards the kidney strengthen the current towards the tissues and conversely, factors that draw the current to the tissues weaken the current towards the kidney. But these currents tend to keep the blood volume and the blood constitution constant as much as possible, and in addition tend to reëstablish the volume and the constitution of the blood after they have been temporarily disturbed; they have therefore a regulatory character. As we stated salts, especially sodium chloride, play a part in this regulative mechanism. There is reason to assume that the protein content of tissues and of the fluid material in the interstices of the tissues, specific organ activities, the excretory cell activities and the permeability of capillaries play likewise an important rôle in these processes. In addition we have found facts which point to the conclusion that certain substances have a specific influence on these currents and may reverse their direction under certain conditions and this experimental reversal of the current we shall discuss still further in a subsequent chapter.

Added to the main currents just mentioned are supplementary ones which play the part of safety currents; they are directed primarily into the peritoneal and pleural cavities and secondarily into the tissue spaces. These cavities play therefore the part of overflow vessels and they are a last safeguard tending to uphold the constancy of the blood composition.

It follows from these statements that a consideration of the composition of the blood alone is insufficient to account wholly for the elimination of substances through the kidney, inasmuch as the amount of water, sodium chloride and other substances present in certain

tissues, as well as certain specific substances which probably alter primarily the permeability of membranes, determine the direction of the current either towards the tissue or towards the blood and kidney.

B. Sodium chloride in its relation to edema

In the preceding chapter we have discussed the significance of salts, especially of sodium chloride, in the movements of water within the organism. In this chapter we shall deal with the effect which sodium chloride and certain other salts have on the development and intensity of edema and on the elimination of the edematous fluid, and we shall attempt to consider connectedly some of the facts to which we have referred above at various places. We shall thus correlate the function of these salts in the distribution of fluid in the normal individual with the same function in the pathologically changed organism.

The knowledge of the relations between salts and edema was established step by step. Bartels and Grainger Stewart believed renal edema to be due to the insufficient elimination of fluid through the kidney and to the subsequent development of hydremic plethora which led to the transudation of water into the tissue spaces. With the advent of physical chemistry, attention was directed, particularly by Koranyi, to the importance of osmotic changes in the causation of edema. He found in nephritis and pneumonia a significant change in the osmotic pressure; it was increased in the blood and diminished in the urine. But in addition this author, in common with some other investigators, was already aware of the special significance of sodium chloride in edema and he held the opinion that the development of edema depended less on the osmotic pressure, as such, than on the relative increase of sodium chloride in the blood, as compared with that of other osmotically active substances. This ratio between sodium chloride and other osmotically active substances was found increased in various conditions and in particular in cardiac incompetency. Other investigators had likewise observed a retention of sodium chloride in various diseases, among which renal affections were prominent. It is, however, mainly due to the work of Achard, Strauss and Widal that the significance of sodium chloride in the development of edema has been generally recognized. Widal found that in certain cases of nephritis the edema increases pari passu with the amount of

sodium chloride given with the food. Conversely, Strauss and Widal showed that the administration of a diet, which contains a minimum amount of sodium chloride, constitutes an efficient treatment of renal edema. Strauss especially emphasized the conclusion that in edema the retention of sodium chloride is the primary condition and that it is followed by the retention of water. This was also shown to be the case in experimental chronic nephritis (Heineke). Widal observed furthermore that edema is preceded by a condition which he called "pre-edema," in which the retained sodium chloride holds back water without as yet causing a visible collection of fluid in the tissue spaces and serous cavities; merely an increase in weight of the individual indicates this preliminary retention of water.

It must however be stated that these views were not generally accepted. Some investigators were doubtful as to the preponderating influence of sodium chloride in edema (Mohr, Blooker, Vogel), especially in view of the fact that a restriction of this salt in the diet did not, in all cases, have a favorable effect on the edematous condition.

Notwithstanding these objections, there can be no doubt as to the very great importance of the retention and distribution of sodium chloride in edema and this importance is now almost generally recognized. This does not apply only to renal edema; thus, according to L. F. Meyer, the addition of sodium chloride aggravates the water retention in infants suffering from so-called idiopathic edema.

There is, however, still some doubt as to the mode of action and the cause of the retention of this substance. Widal and Strauss held that the retention of sodium chloride was entirely due to the inability of the kidney to eliminate it. Ambard, a collaborator of Widal, determined the relative concentration of this salt in the blood and urine, which regulates its excretion, and he found a threshold concentration for sodium chloride in the blood, below which it is not excreted. This threshold is raised in nephritis; it also varies with the concentration of sodium chloride in the blood.

It may be of interest here to state that for urea, in contradistinction to NaCl, a threshold does not exist, and that while according to Widal the retention of urea and other nitrogenous substances is responsible for uremia, they are of no significance in the development of edema, the latter being caused mainly by the retention of NaCl.

Widal assumed furthermore that NaCl injures the kidney tissue, producing a local renal edema and that the withdrawal of sodium chloride from the food may lead to a restoration of the normal condition of the kidney and thus bring about the elimination of the edematous fluid. Widal, Ambard and Weill also concluded that in nephritis sodium chloride is increased in the body, whether edema is present or not. If owing to the rise in the threshold of the kidney for sodium chloride elimination, sodium chloride is retained in the blood to a greater extent than urea, edema occurs. Similarly Strauss considered changes in the kidney to be the primary cause of the sodium chloride retention.

These views of Widal and Strauss as to the exclusive significance of the kidney in the retention of sodium chloride have now been abandoned by the majority of authors. It is known that the retention of this salt may occur in heart disease, in infectious diseases, especially pneumonia (von Hoeslin), as well as in pernicious anemia and in anemia caused by trypanosomes (Christian, Steinfield). Furthermore Achard showed that there is no correspondence between the concentration of sodium chloride in the blood and the intensity of edema. There may on the one hand be hyperchloremia without edema, and on the other hand there may be a normal sodium chloride concentration in the blood with edema, and there may even be hypochloremia associated with a retention of sodium chloride. There is therefore no relation between the capability of the kidney to eliminate sodium chloride and the actual retention of this substance in the blood and the subsequent edema. Achard held therefore that, in the main, tissue changes are responsible for the retention of this salt, and the experiments of Castaigne, as well as other facts, which we have mentioned, or to which we shall refer in later chapters, seem to prove directly the significance of extrarenal factors in the retention of sodium chloride.

We may then consider it as certain that the retention of sodium chloride in the blood is not directly responsible for edema, but rather the retention of this salt in the tissues. The problem which remains to be solved concerns the factors which cause this retention in the tissue. Is it merely the failure of the kidney to eliminate this salt properly which leads to a storing up in the tissues, or, is this process

of tissue retention due not to the retention of the salt as such, but to changes which take place in the blood-vessels or tissues through the action of certain substances produced by the diseased kidney? Or are both the retention as well as a toxic change in blood-vessels and tissues responsible? We must confess that the exact mechanism which leads to the retention in the tissues is hypothetical; we know it occurs in normal individuals under various circumstances, as well as under certain pathological conditions, prominent among which are kidney lesions. The differences under normal and pathological conditions are mainly of a quantitative character affecting duration and intensity of the change. At present it appears most probable that the insufficient function of the kidneys and the subsequent retention of substances leads to alterations in the exchange of these substances between tissues and blood-vessels. That the kidney plays a part in the retention of sodium chloride would also be in accordance with the conclusions of Schlayer, Hedinger and Takayasu, who showed that uranium nitrate not only makes the renal vessels impermeable to sodium chloride and water, but that in addition this effect appears at an earlier date after administration of uranium nitrate, which causes edema, than in the case of chromate or mercury poisoning, which does not usually lead to edema. This impermeability of renal vessels is believed by these authors to be followed by an increased permeability of the cutaneous vessels, which latter is held to be responsible for the anasarca. However, as we have stated above, such an increased permeability of the cutaneous vessels has not as yet been demonstrated in the case of uranium rabbits and has even been made improbable through the experiments of Boycott and Mendel. The recent studies of Blum, Aubel and Hausknecht, to which we referred above, on the other hand, again confirm the intimate relation between the sodium content of the blood and tissues and the amount of water which is retained in the tissues.

As to the constituent of sodium chloride which is responsible for the effect of this substance on the distribution and movement of water, some of the earlier authors, especially Widal and his collaborators assumed that the edema producing effect is to be attributed to the anion chlorine. However, not only sodium chloride but the administration of some other sodium salts and especially sodium bicarbonate

may likewise cause the development of edema. Widal assumed consequently that the ingestion of sodium bicarbonate is followed by a retention of sodium chloride and that the chloride thus retained is the direct cause of edema in such cases. Accordingly, sodium bicarbonate was found to be less effective as an edema producing agent than sodium chloride and a combination of sodium chloride and sodium bicarbonate was more effective than either alone. Labbe and Guerithault, on the other hand, observed that sodium bicarbonate may cause edema without retention of sodium chloride.

Of special interest in this connection are the observations of Pfeiffer, Magnus-Levy and others, who found that in contrast to sodium chloride the administration of potassium and calcium chloride does not cause a retention of water but that these salts are promptly eliminated through the kidney and may even lead to an increased discharge of sodium chloride and may thus diminish edema. This applies to the movements of water in persons with nephritis as well as in normal persons. Moreover, according to Magnus-Levy potassium acetate may lead to the discharge of edema even in cases where diuretin is without effect. It seems furthermore that sodium bromide can take the place of sodium chloride in causing retention of water (Bogendörfer), and, according to Richter, sodium phosphates likewise act similarly to sodium chloride in producing edema in uranium rabbits. In edema due to malnutrition also other sodium salts can take the place of sodium chloride (Hülse).

In acute infectious diseases potassium ions can be promptly excreted, while sodium ions are retained, and according to Limbeck following the crisis in pneumonia, the excretion of sodium ions is much more marked than that of chlorine ions. We must assume that in the latter case other anions have taken the place of chlorine. On the other hand there is the contrary observation of Moraczewski, who states that in pneumonia the chlorine of potassium chloride is retained as well as the chlorine of sodium chloride.

Of particular interest are recent experiments of Blum, Aubel and Hausknecht. These authors put nephritic patients on a salt poor diet and then added alternately corresponding quantities of potassium chloride and sodium chloride. They found both salts to be retained, the sodium retention to be accompanied by an elimination of po-

tassium, while the retention of potassium led to an excretion of sodium. But only a retention of sodium chloride was accompanied by a gain in weight due to the retention of water. Potassium salt did not have this effect. The retention of water is therefore, they conclude, a specific effect of the sodium ion.

All these facts make it very improbable that the chlorine ion is responsible for the retention of water. It is the kation which has this effect and in particular the sodium. Potassium and calcium act differently. Sodium bicarbonate is less effective than sodium chloride, perhaps because the bicarbonate ion is eliminated more readily than the chlorine ion and thus carries with it some of the sodium ions. We may furthermore, for the same reason, assume that if sodium bicarbonate is administered, chlorine ions are substituted for a certain number of bicarbonate ions. It has thus become very probable that in all these conditions it is mainly the kation sodium and not the anion which causes edema.

Does a relation exist between the retention of non-protein nitrogen and edema? In severe cases of nephritis the non-protein nitrogen is increased in the blood (Ascoli, Strauss); especially the urea is is increased but creatinin and uric acid may also be increased (Folin and Denis, Myers and Fine). While under these conditions the percentage increase of urea is greatest in the blood, the greatest total quantity of this substance is found, as we have already mentioned, in the muscle tissue (Becher). An increased quantity of non-protein nitrogen in the blood is likewise found after nephrectomy —an operation which is supposed to stimulate the breakdown of protein—and it is furthermore observed in cases of wound shock (Duval and Grigaut). The recent studies of Klein make it seem probable that in some cases of nephritic and cardiac edema, non-protein nitrogen may be temporarily stored even in the edematous fluid and from here proceed into the blood and subsequently be eliminated through the kidney at the time of the discharge of the edematous fluid. Notwithstanding this fact as we have stated above, no relation exists, as far as we know, between this retention of nitrogenous substances of a non-protein nature and edema; the distribution of these substances may on the other hand possibly be related to the development of uremia. Widal particularly drew attention

to this antagonism between salts whose retention causes edema, and urea, the retention of which may cause uremia.

It may thus be stated that substances, which penetrate as readily into cells and tissue as does urea, are not apt to produce noticeable changes in osmotic pressure and unequal distribution of water, but that the latter may be caused by certain inorganic salts, which penetrate not at all or only with greater difficulty into cells, and tissue substance proper, and that edema is due to a high intensity of such an unequal distribution.

We may conclude that under normal, as well as pathological conditions, it is mainly—but perhaps not exclusively—the sodium ion which determines, through its movements, the movement of water in the body. We have reason for assuming that the effect of sodium in the development of edema is not different from the effect of this substance on the movement and distribution of water in general; it has the special action of producing edema only when under pathological conditions certain factors act in such a way that the abnormal distribution of sodium is increased in duration and intensity. It exerts this function apparently through the same mechanisms through which it acts on the distribution of water in the normal organism. These factors, which change the current of sodium and influence the intensity of this change, are evidently the essential causes of edema and sodium is a realizing factor. As to the mechanism, through which sodium determines the distribution of water, it is probable that it acts mainly through its influence on osmotic pressure in the tissue spaces primarily and in the blood and organs secondarily. How far in addition electro-endosmotic factors come into play in this effect, we do not know at the present time.

It is of interest to consider the reason why this specific action should attach to the sodium ion. It may be due to the fact that sodium is the most common and relatively the most indifferent ion in the body fluids, and that it is normally present in the body fluids in much larger quantity than all the other kations. Associated with this fact is the relative lack of specific effects of this substance. Potassium and calcium, because they are normally present in so much smaller quantities, set in motion mechanisms which lead to their elimination from the body fluids as soon as their quantity becomes abnormal, and thus

they may cause, among other effects, diuresis. Specific organs of excretion are stimulated much less by sodium and so it can produce osmotic effects within the body. We may also have to consider the fact that in all probability the proteins are present in the body fluids largely as sodium proteinates and that this may in part account for the tendency of sodium to be retained under pathological conditions.

XII. THE INFLUENCE OF CAFFEINE AND RELATED SUBSTANCES ON THE MOVEMENTS OF WATER AND SALTS IN THE NORMAL AND NEPHRITIC ORGANISM

The diuretics of the Purine group have in certain cases of edema a noticeable accelerating influence on the discharge of the edematous fluid. It was therefore of interest to determine in what manner these substances affect the movement of water and salts, especially of sodium chloride, in the body. Weber injected salt solutions subcutaneously and intravenously and found, under the influence of caffeine, a more rapid movement of the solution from the subcutaneous tissue into the blood in the first case and out of the blood into the tissue in the second case. Georgopoulos observed an increased absorption of serum injected into the peritoneal cavity under the influence of caffeine; he attributes this effect to a stimulating action of caffeine upon the lining membrane. Fleisher and Loeb undertook the first systematic study of the effects of caffeine on the movements of salt and water under various conditions which are comparable to those which prevail in edema. We analysed the influence of caffeine on the absorption of an intraperitoneally injected solution of 0.85 per cent sodium chloride in normal rabbits, in rabbits which had been previously nephrectomized or in which another operation had been performed, and lastly in rabbits to which uranium nitrate had been administered one or three days previously. The results are as follows: In the series of normal rabbits caffeine increases the secretion of urine through the kidney and raises very considerably the percentage of urinary sodium chloride. At the same time it lowers the sodium chloride content of the blood serum as well as its osmotic pressure. It exerts this effect on the osmotic pressure of the blood serum even in rabbits which have not been previously injected intraperitoneally with a solution of sodium chloride. Caffeine has therefore a specific

effect on the sodium chloride elimination through the kidney. In consequence of this movement of sodium chloride from the blood into the urine, the sodium chloride contained in an intraperitoneally injected solution of this salt moves more actively from the peritoneal cavity into the blood. Caffeine increases therefore the absorption of sodium chloride from the peritoneal cavity, but on the other hand it does not increase the absorption of peritoneal fluid in normal animals, because it lowers the osmotic pressure of the blood. In such animals following an intraperitoneal injection of sodium chloride a dilution of the blood takes place as a result of the absorption of the sodium chloride solution from the peritoneal cavity. Caffeine diminishes this dilution by increasing the amount of fluid eliminated from the blood-vessels through the kidney.

As we have stated above, every operation of sufficient importance, of whatever kind, raises the osmotic pressure of the blood. In animals, which have been operated upon, caffeine is less effective as a diuretic, although it still produces diuresis and it also diminishes the dilution of the blood by increasing the elimination of fluid from the blood-vessels. Under these conditions it not only causes an increased absorption of sodium chloride but even of fluid from the peritoneal cavity, owing to the rise in the osmotic pressure of the blood.

In nephrectomized rabbits the osmotic pressure of the blood is likewise higher than normal and caffeine causes, in these animals, an additional rise in the osmotic pressure. In consequence of this effect it calls forth an increased absorption not only of sodium chloride but also of fluid from the peritoneal cavity; neither the water nor the salt, however, is retained in the blood, but under the influence of caffeine both are transported into the tissues. Caffeine causes therefore an increased elimination of fluid and sodium chloride into the urine, if the kidney functions; if it does not function, it causes an increased elimination of fluid and sodium chloride from the blood into the tissues.

This effect of caffeine applies in a specific manner so far only to sodium chloride. Other osmotically active substances move in the opposite direction, namely, from the tissues to the blood and into the peritoneal cavity. From these experiments we concluded that the action of caffeine in increasing the elimination of sodium chloride

from the blood or peritoneal cavity is not necessarily due to a specific effect of this substance on the kidney; on the contrary the influence of caffeine upon the composition of the blood may in part, at least, account for the caffeine diuresis. As we pointed out at the time of our experiments, the primary change caused by caffeine may consist in calling forth some condition that causes the sodium chloride and water to leave the blood in the direction towards the kidney, if possible, and otherwise in the direction towards the tissues. There are evidently other tissues which attract sodium chloride and water in a manner similar to the attraction exerted by the kidney. According to Erich Meyer and R. Meyer-Bisch the effect of pituitrin is to some extent analogous to that of caffeine. In diabetes insipidus pituitrin causes a movement of water from the blood and lymph to the kidney on the one hand, and to other tissues on the other hand. The experiments of Rowntree and his associates, to which we referred above, also suggest this conclusion.

While caffeine causes thus an increased absorption of fluid from the peritoneal cavity in nephrectomized rabbits, it does not have this effect in animals which three days previously have received a toxic dose of uranium nitrate, although in this condition, too, the osmotic pressure of the blood is raised considerably. As the result of the uranium poisoning, the increase in absorption is lacking notwithstanding the fact that caffeine causes a slight additional rise in osmotic pressure in the blood; secondary factors counteract in this case the consequences which would otherwise follow upon such a rise in osmotic pressure. Still caffeine effects even in such uranium animals, in which no longer any secretion of urine occurs, a slight movement of water from the blood to the tissues.

Quite recently Nonnenbruch observed that under certain conditions theophyllin causes, in addition to an increased movement of fluid and salt, also an increased movement of protein from the tissues into the blood.

If we compare the effects of caffeine with those of adrenalin, we find that both increase the absorption of fluid from the peritoneal cavity, in those cases in which they raise the osmotic pressure of the blood. Adrenalin increases therefore the absorption of water more generally, while caffeine has this effect only under special conditions. Caffeine

increases the diuresis while it does not increase the absorption of fluid from the peritoneal cavity in normal animals; adrenalin on the other hand increases in normal rabbits both the diuresis and the absorption of fluid from the peritoneal cavity. Both these substances cause an elimination of fluid from the blood-vessels. The most marked difference between caffeine and adrenalin concerns their effect on sodium chloride. While caffeine has a specific effect on the elimination of this salt, adrenalin on the contrary increases the absorption of water more than that of sodium chloride. It does not specifically cause the elimination of this salt from the blood-vessels, and therefore diminishes, rather than increases, the quantity of sodium chloride absorbed from the peritoneal cavity with a unit of water. Conversely it does not cause the opposite movement of other osmotically active substances into the blood and peritoneal cavity, as does caffeine. Caffeine eliminates sodium chloride both through the kidney and into the tissues, while adrenalin is inert in both respects. Adrenalin accelerates the movement of water, but only to a slight extent or not at all that of sodium chloride.

The more recent experiments of Veil and Spiro agree well with and are essentially confirmatory of the results obtained by Fleisher and Loeb. Veil and Spiro administered to rabbits a solution of sodium chloride by mouth and obtained a dilution of the blood in nephrectomized animals. In such nephrectomized rabbits administration of theocin caused a movement of water and sodium chloride from the blood to the tissues; from here these substances are presumably eliminated through the action of certain glands.

The kidney and other tissues are thus coördinated. If under the action of theocin the blood has lost much sodium chloride, it is retained in the blood in a period subsequent to the theocin administration, and now the urine on the contrary becomes poor in sodium chloride. If much sodium chloride has previously been stored in the body, as for instance, in cases of cardiac edema, the diuresis and elimination of sodium chloride under the influence of theocin may continue for a longer period of time than in a normal individual, where the tissues become more readily exhausted.

We see then that in the normal organism caffeine causes a coördinated movement of sodium chloride and water from the blood to

the kidney and from the tissues to the blood. Protein also passes from the tissues into the blood. The elimination through the kidney seems under these conditions to be more active than the movement from the tissues to the blood, and the elimination of sodium chloride through the kidney is apparently, under the influence of caffeine, a primary effect in contradistinction to the effect produced by adrenalin on the movement of this substance and of water. If the passage of salt and water from the blood to the kidney is prevented, the movement occurs in the opposite direction, namely from the blood to the tissues. The movement of water and sodium chloride from the peritoneal cavity to the blood is apparently not entirely coördinated with the movement of these substances from the tissues to the blood, but it is a subsidiary movement and to some extent independent of the latter. As we have seen uranium nitrate alters these movements of water and salts completely.

XIII. COLLOIDS AND THEIR SIGNIFICANCE IN THE DISTRIBUTION OF WATER IN THE ORGANISM UNDER NORMAL AND PATHOLOGICAL CONDITIONS

There exist numerous observations in the literature concerning the effect of colloids on the movements of water in the body as well as in vitro. By a simple method Oker-Blum demonstrated this influence in vitro; he showed that the addition of blood serum to the fluid surrounding plates of gelatine prevents water from entering the latter and that the proteins of the serum are responsible for this effect.

From theoretical considerations Starling attributed to the colloids of the blood great significance in making possible the return of fluid from the tissues to the blood-vessels. This author assumed that the greater the difference between the amount of proteins in the blood-vessels, and in the tissue spaces surrounding the latter, the more marked is the movement of water towards the place of greater concentration of proteins. Overton showed that if a colloid is added to the solution in which a piece of muscle is immersed in vitro, fluid may be withdrawn from the muscle. The colloid material in this case attracts water much more strongly than could be foreseen from its

relatively low osmotic pressure. Wessely found that, after an injection of hypertonic salt solutions under the conjunctiva, protein becomes mixed with the injected fluid. He attributes to this fact the slow absorption of an injected salt solution even after it has become isotonic with the body fluid. Similar observations were made by Eppinger after subcutaneous injections of a solution of sodium chloride. This author furthermore showed that the addition of gelatin to a sodium chloride solution causes a great delay in the absorption of the latter. Various investigators established the influence of colloids on the secretion of urine; we shall, however, refer here only to the observation of Ch. Richet who noticed a diminution in the urine after the intravenous injection of a solution of gum. This agrees with the finding of Roger and Garnier and others, that intravenous injections of gum or gelatin cause an increase in the retention of fluid in the blood. The plethora and increase in viscosity of the blood resulting from such an injection may lead to a dilatation of the right heart and to pulmonary edema. In an analogous manner a reduced size of the heart, brought about through hemorrhage or withdrawal of blood, can be restored through an intravenous injection of gum acacia and sugar solution. Ringer's solution on the other hand does not have such a restorative effect (E. Meyer and R. Seyderhelm). M. H. Fischer likewise showed the power of colloids to retain water after intravenous as well as intraperitoneal injection. Boycott and subsequently Bogert, Underhill and Mendel, observed that colloids tend to retard the velocity with which solutions leave the vessels after intravenous injection.

Some recent observations indicate that proteins together with tissue fluid, may spontaneously enter the blood-vessels. If an intravenous injection of 40 cc. of Ringer solution is made with the addition of 6 per cent gum or 5 per cent gelatin, a primary plethora is induced, but the number of erythrocytes again becomes normal at the end of two hours (Nonnenbruch); only if a hypertonic gum solution, similar to that used by Erlanger and Gasser, has been used does a plethora of longer duration ensue. The injected colloids soon enter the tissue and here they may apparently exert an inhibiting effect on diuresis. Within the first two hours the intravenous injection of gum solution calls forth a decrease in the erythrocyte count, owing to the entrance

of fluid into the blood-vessels. According to Nonnenbruch this fluid contains protein; therefore the diminution in the number of erythrocytes in the first two hours is found to be much greater than the loss in serum protein. His calculations indicate that fluid containing about thirty percent of protein enters the blood stream. This stage is followed by a loss of protein (hypalbuminosis) which still persists after the return of the blood corpuscle count to its normal figure. Intravenous injection of a solution free from protein likewise causes the entering of protein into the blood. This again is followed by an excess loss of protein from the blood, after the injected fluid has been eliminated. Similarly after a loss of water through perspiration proteins may enter the vessels together with the tissue fluid (Gron and Kestner, Cohn, Bogendörfer). We have already referred above to the action of colloids in shock (Hogan, Bayliss, Erlanger and Gasser).

The significance of colloids in edema is suggested by the fact that edematous fluids contain proteins and that, in certain cases, factors, which increase or call forth edema, increase at the same time the protein content of serous cavities or tissue spaces. The protein content of the edematous fluid is especially great in inflammatory edema, as for instance, in pneumonic exudate. In rabbits with peritonitis, Fleisher and Loeb found that the absorption of salt solution injected intraperitoneally did not take place, notwithstanding the high osmotic pressure of the blood in these animals. On the contrary, substances which tended to increase the osmotic pressure of the peritoneal fluid were attracted into the peritoneal cavity. Even in nephrectomized rabbits and in rabbits treated with uranium nitrate the peritoneal fluid contained a larger amount of protein than in normal animals. There is a possibility that this increased protein content is at least partly responsible for the diminished absorption of fluid from the peritoneal cavity following the administration of uranium nitrate. In accordance with these findings various authors and especially M. H. Fischer and Eppinger, have attributed great importance to the presence of colloids in the development of edema, as we shall discuss more fully in subsequent chapters.

As might be expected the fluid withdrawn in anasarca contains protein. The quantity of protein varies however in different cases. Beckmann made comparative studies of the protein content of various

edematous fluids withdrawn from the subcutaneous tissue. In glomerulo-nephritis the fluid was richest in protein; it was less so in cardiac edema and in other edema due to mechanically produced congestion; although in these cases the protein content was still relatively marked. The protein content reached its lowest level in war edema and in edema following nephrosis and amyloid kidney. It is of interest that the sodium chloride content of the edematous fluid did not run parallel to the concentration in protein, and further that no relation existed apparently between the amount of edematous fluid retained in the patient and the concentration of the fluid in protein. With these findings agree the recent studies of Haas. According to this author the protein content is highest in acute glomerulonephritis. In kidney lesions of a degenerative character (nephrosis) and in cardiac edema he finds a low or medium concentration of protein. R. F. Loeb, Atchley and Palmer likewise noted a low concentration of protein in ascitic fluid in cirrhosis of the liver and in renal edema—presumably cases of nephrosis or non-acute nephritis—while in cardiac and cardiorenal disease the protein content was higher. In general Haas does not find a parallelism between the severity of the edema and the protein content of the edematous fluid. Only in the pure forms of cardiac edema does such a parallelism exist. We may assume that in the latter condition the amount of edematous fluid and the concentration of protein in the fluid depend upon the retardation in the capillary circulation and upon the increase in permeability of the capillaries, and that this increase in permeability is to a certain extent proportional to the circulatory disturbance. As a rule the great variability of protein concentration depends presumably upon corresponding variations in the permeability of the blood capillaries. Haas confirms the conclusion, to which we referred above, that an increased amount of protein in the edematous fluid is not noticeably associated with an increased amount of sodium chloride. Likewise a high protein content does not prevent a rapid discharge of the edematous fluid. Whenever in cardiac edema the circulation is restored, the elimination of the edematous fluid occurs independently of the amount of protein present in the fluid. Similarly in edema accompanying glomerulonephritis, in which the fluid contains much protein and in which the blood pressure is high, a rapid discharge

may take place concomitant with the fall of the blood pressure; while a slight edema with a low protein content may persist a long time, provided the kidney lesion persists. The protein does not prevent absorption of the edematous fluid.

More recently Gayda and subsequently Ellinger studied the conditions which lead to the production of edema by perfusing blood-vessels of frogs in the Laewen-Trendelenburg or similar preparations with various kinds of fluids. These authors confirm to a certain extent the significance of colloids in edema. They find that the hypertonic solutions of salts or anelectrolytes either prevent edema or they may withdraw fluid from the edematous and even from the normal tissues. Pure serum also was found particularly effective in this respect. Gayda assumes the presence in the serum of two active substances, one coagulable through heat, the other not coagulable; to the latter we have referred in an earlier chapter, in our discussion of the factors which influence the contraction and permeability of capillaries. Correspondingly injection of serum into the muscle tissue of the perfused frog causes here a localized edema and serum injected subcutaneously attracts fluid from the blood-vessels, if the latter are perfused with Ringer solution (Ellinger and Heymann).

The edema in nephrosis is attributed by Epstein to a diminution in the protein content of the blood which results from the loss of this substance through the kidney. In accordance with the conception of Starling he assumes that in consequence of this diminution in protein content the osmotic attraction of the blood for water decreases and that the water, which would otherwise have passed into the blood, is retained in the interstices of the tissues.

As we shall discuss later, through combination with acids or bases, the water binding power of the proteins is increased. Ellinger and Heymann could accordingly show that serum which had been dialyzed against an acid or alkaline solution attracted water, in perfusion experiments, with much greater intensity than did ordinary serum.

Of great interest is also the observation of these authors that perfusion of the eviscerated frog with distilled water leads to an imbibition of the muscle tissue proper, while perfusion with isotonic salt solutions is followed merely by a collection of the fluid in the tissue spaces. It is possible to withdraw again edematous fluid from the tissue spaces

through perfusing the vessels with hypertonic salt solutions or even more actively with hypertonic solutions of cane sugar; still more effective was a perfusion with a 2 per cent solution of gum made up with Ringer's solution. Now, the edematous fluid, as it occurs spontaneously, represents an isotonic salt solution and not distilled water. We may therefore conclude that the edematous fluid will collect in the tissue spaces rather than in the parenchyma of organs proper.

Ellinger and Heymann assume that the osmotic pressure exerted by the protein solutions plays a minor part in attracting water and that it is rather the imbibition pressure of either protein sols or gels on which depends their water binding power. The total water binding power of protein solutions is much greater than could be foretold from an estimation of their osmotic pressure. According to these authors the following factors determine the development of edema in the tissues: (1) the amount of protein present, (2) the combination of protein with acid, and (3) the effect of hormones like thyroid extract which, according to their opinion, exerts an influence on the water binding power of the proteins.

We see that there is reason for attributing a certain influence to the colloids, especially proteins, in determining the development and intensity of edema, although it is as yet doubtful whether this influence is as great as some authors assume. However that may be, it will be necessary for us to inquire somewhat more in detail into the factors that determine the water attracting power of proteins.

In the interpretation of edema the relation of salts to the water binding power of proteins is of special importance. Hofmeister was the first author who investigated this relationship. He found that certain salts diminish, while others increase, the swelling of solid proteins and he arranged anions and also kations in a definite order according to their influence on the water attracting power of protein. A somewhat similar order of ions was subsequently found in various other processes affecting the functions of cells and tissues. Subsequently Spiro showed that acids increase the swelling of proteins and in varied experiments M. H. Fischer determined the antagonistic effect which salts exert on the swelling of the proteins under the influence of acids or alkalies. In accordance with the Hofmeister series, Fischer found a great difference in the effectiveness of various

salts in preventing the swelling of proteins under these conditions, and he recommended therefore certain salts as particularly valuable in the treatment of edema. A. D. Hirschfelder showed however that the differences found by Fischer in the action of various ions are not direct effects of these ions, but depend on the hydrogen ion concentration under which their action takes place. If the hydrogen ion concentration is kept constant, different neutral salts are identical in their action with the exception of sulphates, which depress the water binding power of proteins more than other salts.

The great significance of the hydrogen ion concentration in protein solutions, as a factor in their water binding power, has recently been analysed in a series of investigations by Jacques Loeb and here, furthermore, a beginning has been made in the separation of the various factors which might participate in causing the affinity of proteins for water, which has so far largely been attributed to adsorption. Thus it will be seen that in all probability forces of different character coöperate in bringing about what is usually called the imbibition pressure of proteins.

Three characteristics of proteins are of importance in this analysis. In the first place proteins are amphoteric; they combine with the anion as well as with the kation to form salts, in which the protein molecule furnishes the complementary ion. The hydrogen ion concentration of the solution determines which kind of salt shall be formed. In an acid solution in which the hydrogen ion concentration surpasses that concentration which is characteristic of the isoelectric point of that particular protein, the protein furnishes the kation and the acid the anion. With hydrochloric acid, for instance, protein forms a protein chloride. In an alkaline solution the opposite protein salt forms, namely, a proteinate in which the base provides the kation and the protein the anion. At the intermediate point, the so-called isoelectric point, in which the solution is neither acid nor alkaline as far as the protein is concerned, the protein combines neither with the anion nor with the kation. It does not form salts but exists as a non-iogenic molecule. These conceptions are based on the investigations especially of Michaelis, Sorensen and Jacques Loeb. The latter particularly completed the proof of their general applicability and we shall follow his presentation of the subject. At the isoelectric point

the protein has the minimum of water binding power; the more the acid or alkali that is added to this solution, the greater becomes the water attracting power up to a certain maximum, when a further addition of acid and alkali diminishes it again. Such a relation between ionization of the protein and its water attracting power had already been indicated by Laqueur and Sackur, but the correct interpretation was first given by Jacques Loeb who showed that it is due to the Donnan membrane equilibrium, which develops when a membrane separates a set of ions, one of which cannot diffuse through the membrane, while the other ions can do so. This represents the second characteristic of proteins which they have in common with all substances whose molecule is very large. Thus water is attracted from the outside of the membrane and the more so the greater the amount of acid or alkali which has been added to the protein solution up to a certain maximum, when further addition again depresses the water attracting power. Protein solutions therefore surrounded by a membrane exert osmotic pressure. This osmotic pressure is however only in a relatively small degree due to the protein ions themselves; it is mainly caused by the diffusible ions, which, according to the Donnan equilibrium, are present in a surplus inside of the membrane.

As R. S. Lillie has shown, salts added to the protein solution depress its osmotic pressure. According to Jacques Loeb this is again due to the effect of the salts on the Donnan equilibrium, which latter causes a diminution in the excess of diffusible ions within the membrane. We have therefore in this case to deal with an indirect action of the salts.

But proteins have still a third property, in common with other colloids, namely, that of forming larger aggregates of ions or molecules, micellae, emulsified or suspended particles; the latter have a special water binding activity, which, as Jacques Loeb, in accordance with the findings of Procter and Wilson, has shown, is also regulated by the Donnan equilibrium. It is due to the fact that the protein molecules or ions in the micella, in contradistinction to the diffusible ions, cannot move freely. In this case the Donnan equilibrium is influenced by the same factors which affect the osmotic pressure; in particular, it is depressed by the addition of salts and with this depression in the osmotic pressure goes hand in hand a depression of the water attracting power of the colloid solution. Exceedingly large

amounts of water are thus included in such micellae and the greater the number of micellae and the more water the latter include, the greater becomes the viscosity of these protein solutions. This viscosity is determined therefore by the Donnan equilibrium. If the protein micellae become very large a gelatinization of the solution may take place. In this case the water binding power of the gel is again determined by the equilibrium.

Wherever a Donnan equilibrium is present, a potential difference develops either between the solution of a colloid inside and the fluid on the outside of the membrane, or between the gel or micellae and the surrounding fluid. The size of this difference in potential is again quantitatively determined by the Donnan equilibrium and it is altered by the addition of salts in the same direction as the equilibrium. It is always the ion with a charge opposite to that of the protein ion in the protein salt which has the depressing effect, just as, according to Hardy, the opposite ion has the power of precipitating colloids in suspension. In both cases the effect of this oppositely charged ion increases rapidly with increasing valency.

In case water moves through the pores of a membrane of protein character, potential differences may originate between the water and the membrane, which according to Jacques Loeb are again due to a Donnan equilibrium, developing between the non-movable constituent of the membrane and the diffusible ions. Under these conditions the water assumes a charge which is opposite to that of the protein ion. The electric charge of the water may influence the direction and rapidity of movement of water through the pores of the membrane. Thus if in the solution within a membrane, ions with a certain charge predominate, the solution may either attract or repel the water; ions with a charge opposite to that of water attract the latter, while ions with the same charge repel it. This becomes apparent however only when low concentrations of the salts are used, otherwise the purely osmotic effects obscure these electrostatic influences.

In addition to these factors which are largely determined by the Donnan membrane equilibrium, molecules or ions of protein may attract water by other means, which are probably chemical in character and similar to those which determine the solution of electrolytes in the solvent. These forces and perhaps other factors of a different

kind may come into play even in case the protein is at or near the isoelectric point. Thus isoelectric gelatin in the gel state may take up considerable amounts of water.

The last named category of interactions between the water and proteins, in which the Donnan equilibrium does not play any part, are mainly responsible for the state of solution or precipitation of the latter substances. Especially bivalent anions like SO_4 may have a precipitating effect on the protein, irrespective of the charge of the protein ion. This precipitating effect is greatest near the isoelectric point where the tendency to form aggregates of molecules is usually great. However, in the case of different proteins the different ions may have specific effects, as far as their influence on solution and precipitation of the protein is concerned; and under certain conditions bivalent kations may increase the solubility of some proteins.

We may summarize, in accordance with the conclusions of Jacques Loeb, the factors which come into play in the interaction between proteins and water as follows: (*a*) There is a peculiar distribution of the diffusible ions which cause the movement of molecules of water into a solution of proteins, separated from the outside solution through a membrane. The blood-vessel wall, as well as probably the membranes surrounding all organized structures in living organisms, have to be considered in this connection. But in the living organism complicating factors which influence the movement of water and dissolved substances frequently come into play. In this connection we may recall for instance the fact to which we referred in a previous chapter that membranes, separating the peritoneal and pleural cavities from the surrounding tissues, follow laws which are different from those holding good in the case of the intestinal wall. (*b*) Whenever aggregates of ionized proteins are formed, differences in the distribution of diffusible electrolytes outside and inside the micellae call forth a higher osmotic pressure inside the micellae than outside. Thus great amounts of water become occluded in the interior of the micellae. It is of importance in this connection that different proteins differ much in their tendency to form micellae. We may assume that the tendency to form such aggregates is much greater in the fibrinogen than in the serum albumin fraction. This source of water attraction acts within the solution; a separating membrane not being required

for this purpose. (*c*) The factors, which determine, in general, processes of solution, apply also to isolated protein molecules and ions. These forces are apparently related to those on which depends chemical affinity. Isolated protein molecules near the isoelectric point, as well as protein ions and also aggregates of isoelectric protein molecules may bind water by these means, and we must assume that each molecule of protein may bind multiple molecules of water. (*d*) It is possible besides that physical forces of capillarity may draw water into large micellae of protein. Protein solutions differ in their water attracting power from solutions of readily diffusible substances through the factors mentioned under *a*, *b*, and *d;* and these combined represent what is often called imbibition pressure. If in addition to the action of the imbibition pressure one molecule of protein may by means of its chemical affinities bind more than one molecule of water, it is clear that the water attracting power of proteins is much greater than could be calculated from the osmotic pressure of protein molecules present in solution. The number of protein molecules in solution must be relatively small considering the large size of each individual molecule.

It becomes thus understandable that the proteins play a part in the distribution of water in the body under normal as well as under pathological conditions and particularly in edema. Starling and Bayliss especially have appreciated the significance of proteins in this respect. In recent years M. H. Fischer and Eppinger attributed great importance to the rôle which proteins play in the development of edema. But while Fischer had in view mainly the proteins of organs proper, Eppinger attributed the greatest significance to the protein in the interstitial tissue spaces.

In the foregoing we have found two sets of facts which we must correlate with each other. In the first place, the analysis of edema has established the great importance of salts, especially of sodium chloride in the development of this condition, and secondly we have seen that salts interact with the proteins mainly by depressing the attraction of proteins for water or by influencing the precipitation or solution of proteins. For our purpose we have mainly to consider the depressing effect. In this respect ions act differently according as to whether the protein is an anion or kation. In the living organ-

ism the proteins circulating in the body fluids are as far as they are ionized, in combination with kations; they play therefore the rôle of anions; thus it must be assumed that kations depress their water attracting power and the more so, the higher the valency of the kation. We should then expect that sodium, potassium and calcium would all depress the water attracting power of proteins and act favorably in edema. But in reality we notice on the contrary that, in general, sodium has the tendency to increase edema and to prevent the discharge of the edematous fluid; while potassium and under certain conditions even calcium have usually an opposite effect. If, as we have seen, in specific instances calcium may increase ascites we have in this case in all probability not to deal with a direct effect of the ion on proteins. Neither can the effect of colloidal membranes, and particularly of protein membranes, on the movements of water, and the electrostatic forces which come into play in this process, satisfactorily explain the effect of salts in edema, as far as we understand the factors at work in this condition. Again, we must assume that the proteins forming part of the membranes are mainly metal proteinates. Water would therefore have a positive charge and be attracted by anions. Yet we know that in edema the kations are the more important constituent of salts, as far as their influence on edema is concerned. The fact that neutral isotonic salts in general cause a swelling of collagen, does not satisfactorily explain the effect of salts in edema.

It thus becomes very probable that the salts exert their influence on the development of edema essentially independently of the proteins probably through purely osmotic influences, and that the proteins are concerned in the development of edema only in a secondary way; they become of importance only if primary factors regulating the distribution and elimination of water have become faulty. Proteins play therefore, as far as their rôle in edema is concerned, a part somewhat analogous to that played by salts. Neither of these substances initiates edema, but both play a part subsequently in the development of edema.

Proteins are only one of many factors producing an effect on edema, as they are likewise only one of many factors concerned in the normal distribution of water in the body. According to our present knowl-

edge it would be impossible to consider the influence of proteins as the preponderating factor. Whenever in an individual case the particular causes of edema are removed, the edematous fluid is discharged regardless of the amount of protein it contains. Protein can evidently be readily eliminated from the tissue spaces by the normal organism.

XIV. THE SIGNIFICANCE OF HORMONES IN EDEMA

While the significance of salts in the development of edema has attracted the attention of investigators for a considerable number of years, the conception that hormones may also play a part in this process is of more recent origin and it is mainly to the investigations of Eppinger that we owe this addition to our knowledge. Eppinger found that in many cases of edema, especially in edema due to the so-called myodegeneration of the heart, to nephrosis, acute and subacute nephritis and chronic nephritis—provided in the latter cardiac symptoms are not yet threatening, and the non-protein nitrogen in the blood is still relatively low—the administration of thyroid gland may lead to the discharge of the edematous fluid even in cases in which other modes of treatment are ineffective. In normal individuals thyroid does not act as a diuretic, neither does it strengthen the effect of caffeine, but following oral or subcutaneous injection of water or sodium chloride solution, thyroid administration causes a more rapid elimination of both of these substances. On the other hand, after thyroidectomy elimination of these substances is much delayed. Patients suffering from Graves' disease behave like individuals receiving thyroid tablets; myxedematous patients, on the contrary, are comparable to thyroidectomized animals. While in cases of inanition and fever the elimination of sodium chloride is generally delayed, in nephritis and Raynaud's disease it is much delayed only after subcutaneous administration of sodium chloride, but after oral administration it may be normal. In cases of nephrosis on the other hand it is diminished after both subcutaneous and oral administration, while in compensated heart disease it is normal.

After subcutaneous injection of a sodium chloride solution, the elevation in the subcutaneous tissue caused by the injected fluid remains noticeable much longer in nephritic and myxedematous patients

than in normal persons and in persons suffering from Graves' disease. In cases of inanition the elevation disappears soon; yet the fluid and salt are retained in the body. Subcutaneous injection of hypertonic salt solution leads to the appearance of protein in the fluid and this is probably the cause of the delayed absorption of such a solution. In thyroidectomized dogs protein becomes mixed with the fluid even after injection of an isotonic sodium chloride solution, and this may be also in this case a contributory factor in the slow absorption, as in other cases in which a deficiency in thyroid activity is present.

After hemorrhage a fluid, relatively poor in protein and rich in sodium chloride, moves from the tissues into the blood. In thyroidectomized dogs and in myxedematous persons this movement is delayed. Under the same condition fluid enters the blood and dilutes it also in cases of nephritis, but subsequently sodium chloride is retained in the blood-vessels.

Eppinger interprets these facts as follows: In conditions which lead to edema or myxedema, the permeability of the blood-vessels is increased. In consequence of this alteration the fluid in the interstices of the tissues is richer in protein than usual. This leads to the retention of water and sodium chloride in the tissues and thus to edema. Administration of thyroid causes an increased cell metabolism and in consequence the cells destroy more actively the proteid which collects in the tissue spaces; thus this cause of edema is eliminated. In general Eppinger assumes in agreement with Asher's theory of lymph formation that conditions which increase organ-activity increase thereby the quantity of lymph and the elimination of interstitial fluid in the affected area.

Whatever the correct interpretation may be, there is no doubt about the marked effect of thyroid on the distribution of fluid in the body. In experiments which Hoover carried out in our laboratory several years ago he found that in guinea pigs suffering from marked inanition a certain amount of fluid usually collects in the peritoneal cavity, while it is absent in the large majority of animals in which the same or even a greater amount of inanition has been produced through the combined effects of thyroid feeding and a diminution in the intake of food. It is furthermore very probable that thyroid substance acts primarily not on the kidney but on the intermediary distribution

of salts and water; in a similar manner we found previously indications that caffeine does not influence salt and water movements exclusively through its effect on the kidney. Other observations likewise agree with Eppinger's findings. Thus Ruchti found that thyroidectomy in rabbits not only diminishes the amount of carbon dioxide but also the amount of water given off in the respiratory air, and that a simultaneous thymectomy intensifies and prolongs this effect. Of interest in connection with Eppinger's observations, are likewise the findings of Tatum, that complete thyroidectomy in young rabbits may lead, among other changes, to a hydropic condition in heart, liver and kidney cells. This may be followed by a more general interstitial edema and ascites, which latter Tatum considers as secondary to weakness of the heart action.

The result observed by C. Hart and E. Uhlenhuth, that tadpoles fed with thyroid gland become edematous, is probably due to conditions of a different character. According to Hart it is brought about by degenerative processes which take place in the thyroid gland in such larvae. The condition in the larvae is therefore in certain respects analogous to the myxedematous condition in the fully developed organism.

We may also refer to the findings of Deutsch that in myxedema the concentration of proteins in the blood is increased and that thyroid feeding diminishes it. These findings might be taken to support Eppinger's interpretation of the action of the thyroid in edema.

Quite recently however some interesting facts have been published which suggest a different interpretation of the action of the thyroid on the movement of water and its influence on edematous fluid. Ellinger showed that substances which increase the elimination of water, like thyroid gland, caffeine and certain salts, diminish the attraction which proteins exert on water; they reduce the "imbibition pressure" of proteins and thus make water available for excretion through the kidney. Ellinger demonstrated this effect in experiments in which he perfused the Laewen-Trendelenburg frog preparation with various fluids and also through ultrafiltration.

Of still greater significance are perhaps experiments carried out by Embden and his associates, which indicate that thyroid extract, when added to certain solutions, increases the rapidity with which the

latter pass in vitro through a membrane of frogskin. A substance given off by the thyroid gland may therefore apparently increase the permeability of membranes and for this reason accelerate the elimination of fluid from the tissue spaces. Recent experiments in Asher's laboratory in which it was shown that, under the influence of thyroid, methylene blue passes more rapidly from the body fluids into glandular structures in the membrane nictitans of the frog, suggest a similar interpretation. Thyroid substance would thus have an effect opposite to that of calcium chloride and adrenalin.

It is probable that substances present in other glands with internal secretion also exert an influence on the distribution and elimination of water. In this connection we have to consider especially the posterior lobe of the hypophysis, which affects not only the secretion of urine, but also the elimination of water through the wall of the stomach. E. Pohle found that in frogs in which the hypophysis has been extirpated, both the elimination of fluid through the kidney and the taking up of water through the skin is diminished. In consequence of this disturbance in the exchange of fluid, hypophysectomized frogs become edematous; there is noticeable not only a marked edema of the skin, but in addition the lymph spaces are filled with water. Pohle assumes therefore that the secretion of the pituitary gland affects the exchange of water in general.

In agreement with this conclusion is the effect of pituitary extract on the exchange of water in diabetes insipidus, where it not only diminishes the excretion of fluid but increases the elimination of sodium chloride through the kidney, and therefore the concentration of the urine; but in addition it affects the intermediary exchange of water. As we have stated above, in diabetes insipidus, under the influence of pituitrin, water leaves the blood and perhaps also the lymph vessels and enters the tissue spaces. The effect of pituitrin is therefore analogous to the action of caffeine in nephrectomized animals, which we have discussed previously.

Yet there is no indication that pituitrin increases the permeability of blood-vessels. On the contrary Krogh and Rehberg demonstrated the opposite effect of pituitrin. According to these authors if the legs of frogs are perfused with Ringer's solution, to which has been added 3 per cent gum arabic and red corpuscles, under the influence

of this solution the tonus of the capillaries is lost, the capillaries dilate and pari passu their permeability increases and the perfusion fluid leaves the vessels. If now a very small amount of pituitrin is added to the perfusion fluid the tone of the vessels is restored and the permeability again becomes normal. Previously Krogh and Harrop had shown that under normal conditions the blood serum contains a substance which maintains the capillary tonus. Krogh and Rehberg have made it seem very probable that the internal secretion of the pituitary gland is the substance which functions in this way.

Other parts of the nervous system may also influence the movements of water. They act, according to Pohle, mainly through their effect on the circulation; dilatation of the blood-vessels in the skin and kidney following, for instance, the section of the anterior nerve roots of frogs, leads to increased absorption of water through the skin and to increased elimination through the kidney.

In conclusion we may state that various substances of a hormone character influence the exchange of water and salts not only between blood and kidney, but also between tissues and blood, and that under certain conditions such substances may even reverse the direction of the movement of salt and water. Intimately connected with this effect on the movement of water and sodium chloride is the effect which the thyroid hormone exerts on the elimination of a localized, experimentally produced excess of fluid, in cases in which pathological changes exist that tend to the development of edema. Under these conditions certain hormones may likewise accelerate the absorption and elimination of an excess amount of fluid.

XV. THE COMPOSITION OF EDEMATOUS FLUID

In this chapter we wish to discuss very briefly some of the more important facts, bearing on the chemical constitution of edematous fluid.

Qualitatively the constituents of the edematous fluid are similar to those of the blood, but quantitatively some interesting differences are found. We have mentioned previously that the amount of protein in the edematous fluid differs according to the disease in which edema develops. In general the percentage of protein is higher in inflamma-

tory edema than in edema caused by venous obstruction, but considerable variations occur in individual cases. In edematous conditions of the skin the protein content in inflammatory lesions is likewise higher than in non-inflammatory lesions. It seems that in inflammatory processes the amount of globulin and especially of euglobulin is, at least in some cases, higher in the edematous fluid than in non-inflammatory cases. We have already in a previous chapter considered in greater detail the protein content of certain non-inflammatory edematous fluids.

According to various authors the sodium chloride concentration is frequently greater in the edematous fluid than in the blood. This applies to the renal and cardiac edema of man as well as to the edematous fluid in uranium nephritis in rabbits. It seems that at the time when the discharge of the edematous fluid begins, the sodium chloride is eliminated in larger quantities from the edematous fluid than from the blood; at that period the concentration of sodium chloride may become temporarily greater in the blood serum than in the edematous fluid. In a similar way the edematous fluid in war edema is, according to Hülse, richer in sodium chloride than the blood. This author furthermore finds that in edema due to undernourishment, administration of sodium bicarbonate leads to an increase of this substance in the peritoneal transudate simultaneously with an increase in sodium chloride. He assumes that sodium bicarbonate pushes the sodium chloride into the tissues in a direction contrary to the osmotic potential.

It must be stated however that the majority of these conclusions suffer from the fact that they are based merely on chloride determinations, it being assumed that sodium and chloride ions are always present in equivalent amounts. As we shall see below this does not altogether hold good. Various authors have recently determined the sodium separately from the chloride. Thus Blum, Aubel and Hausknecht showed that the concentration of sodium is increased in the ascitic and in the edematous fluid in general as compared with that of the blood. Whenever the kidney does not permit a sufficient elimination of sodium to take place, it passes into the peritoneal fluid and, according to these authors, the movement of sodium determines always a parallel movement of water.

Various authors have attempted to explain the difference in the distribution of sodium chloride in the blood serum and in the ascitic fluid. Thus Rona at first referred it to the different concentration of proteins in the blood and in the edematous fluid. He assumed that only water can serve as a solvent for the sodium chloride; and the protein content, being greater in the blood than in the edematous fluid, less water would be available in the former for the solution of the salt; the concentration of sodium chloride would thus be greater in the ascitic fluid than in the blood serum. This interpretation presupposes a variation in the concentration of sodium chloride in edematous fluid inversely proportionate to the concentration of protein. In subsequent studies of the distribution of the sodium and chlorine ions, in case blood serum is separated by a membrane from distilled water or from a diluted solution of electrolytes in water, Rona and György concluded that in the blood serum about 10 to 15 per cent of the sodium is combined with protein in the form of a sodium proteinate solution and that if the hydrogen ion concentration of the solution is on the acid side of the isoelectric point of the protein, a salt is formed in which the protein is the kation. Thus an unequal distribution of the diffusible ions occurs on both sides of the membrane corresponding to Donnan's membrane equilibrium. Inasmuch as in normal serum we have to deal with a Na proteinate solution, there would be inside the membrane a greater concentration of chlorine ions.

It is of interest to compare with these conclusions of Rona and György the recent findings of R. F. Loeb, Atchley and Palmer. These authors determined the relative values for sodium and chlorine in blood serum and in edematous fluid and they found the chlorine ion to be more concentrated in the edematous fluid, while the concentration of the sodium was approximately the same in both the blood serum and the edematous fluid. The concentration of calcium was also the same in both, but potassium showed throughout a higher concentration in the blood serum. In accordance with the expectation the differences in the concentration of the chlorine ion in the serum and in the ascitic fluid were inversely proportionate to the concentration of the proteins in both fluids. These are to our knowledge the first comparative determinations of potassium in the blood

serum and in the edematous fluid and the constant difference in the distribution of this substance in these two fluids is of great interest. A definite membrane equilibrium seems thus to exist between chlorine and protein on the one hand and potassium and sodium on the other hand in the edematous fluid and the blood serum; and this equilibrium does not depend upon vital tissue activities, inasmuch as it remains unaltered, according to the same authors, if the two fluids are separated in vitro by a collodion membrane.

The osmotic pressure of the edematous fluid is about the same as that of the blood serum or only a little lower (Bottazzi, R. F. Loeb, Atchley and Palmer). Lymph, on the other hand, has a higher osmotic pressure than blood serum (Hamburger), and organ extracts have a still higher osmotic pressure. According to Collip, non-electrolytes are concerned in the high osmotic pressure of organ extracts to a greater extent than in the case of the body fluids. Sugar, urea and non-protein nitrogen in general are present in similar concentrations in edematous fluid and in blood serum (Denis and Minot, R. F. Loeb, Atchley and Palmer). However, the recent investigations of Otto Klein have made it seem probable that in certain cases of cardiac and renal edema non-protein nitrogen may accumulate in the edematous fluid. According to Jansen the tissue fluid and blood serum have likewise an equal concentration of non-protein nitrogen and also of sodium chloride. In edematous persons suffering at the same time from gout, uric acid varies in equal ratios in blood serum and edematous fluid (Beckmann, Thannhauser), but the concentration of this substance may be greater in the blood serum (Thannhauser).

Palmer, Atchley and R. F. Loeb have shown that the conductivity of the edematous fluid depends upon its protein content. According to these authors protein near the isoelectric point lowers the conductivity while protein, when combined with acid or alkali to form a salt, increases the conductivity. Inasmuch as at the hydrogen ion concentration of the edematous fluid a great part of the protein is non-ionized, the conductivity of the edematous fluid decreases concomitantly with an increase in proteid content. It varies therefore in different kinds of edema in contradistinction to osmotic pressure which is rather constant. The hydrogen ion concentration of edematous fluid and of normal subcutaneous tissue fluid is similar to that

of blood serum. Likewise the concentration of the HCO_3 is the same in edematous fluid and in blood serum (R. F. Loeb, Atchley and Palmer). On the other hand, if excessive work leading to exhaustion is done, the fluid in the spaces separating muscle fibers becomes acid (Schade). In the pus of acute inflammation also we find what Schade calls a hydrogen hyperionia, the pH being on the acid side; this is accompanied by increased carbondioxide tension and a diminished power of the fluid to bind carbondioxide. These facts will be of interest in considering the possible rôle of hydrogen ion concentration in the development of edema. We shall discuss this problem in the next chapter.

If we inject intraperitoneally into normal rabbits a 0.85 per cent solution of sodium chloride the osmotic pressure of this fluid becomes higher than that of the blood in the course of a few hours (Fleisher and Loeb), but we found that if we inject the same fluid into rabbits which have previously been nephrectomized or which have received an injection of uranium nitrate one or three days previously, or in which merely an incision has been made into the thoracic wall, the osmotic pressure is higher in the blood than in the peritoneal fluid at a corresponding period of time. In normal animals which have received an intraperitoneal injection of a sodium chloride solution, other substances than sodium chloride move probably from the blood into the peritoneal cavity, in accordance with the higher concentration of these substances in the blood. This movement occurs apparently at a more rapid rate than the reverse movement of sodium chloride. In animals which have received uranium nitrate three days previously the normal exchange of substances between blood and peritoneal cavity is interfered with, as we have shown in a preceding chapter.

As we have stated above membrane equilibria, which are due to the unequal distribution of protein salts on both sides of the membranes separating edematous fluid and blood and lymph, play also a part in determining the concentrations of various ions in the edematous fluid as compared with blood and lymph. A definite membrane equilibrium is presumably likewise established between the edematous (or interstitial) fluid and the organ content; in this case the cell boundaries play the rôle of the separating membranes.

XVI. EDEMA AND ACIDOSIS

The term acidosis may signify either of two conditions, (1) a change in the buffer system of the blood towards the acid side; such a change leaves the hydrogen ion concentration of the blood unaltered, or (2) a change in the hydrogen ion concentration of the blood in the direction towards the acid side. There is therefore a certain ambiguity attached to the term acidosis which could be avoided in either of two ways. The first of the two conditions mentioned might be designated as a diminution in the blood alkali or as an increase in the H_2CO_3 of the blood; either of these two changes is compensated for through secondary mechanisms in such a way that the hydrogen ion concentration of the blood remains unchanged. The second condition would then represent a true acidosis in which the hydrogen ion concentration of the blood is actually increased. Or secondly we might distinguish between a compensated and an uncompensated acidosis.

The term acidosis was first used at a time when these various possibilities in the regulation of the hydrogen ion concentration had not yet been sufficiently analyzed; at that time a diminution in the alkali reserve of the blood due to an increase of the acids in the circulating body fluids was the condition generally called acidosis. According to L. Henderson the ratio $BHCO_3 : H_2CO_3$ is a measure of the hydrogen ion concentration of the blood. On the whole subsequent determinations have confirmed this conclusion, although this ratio may perhaps only be approximately correct. An increased hydrogen ion concentration in the blood may be produced through an increased production of acid in the body, through an increased introduction of acid into the body from the outside, through a diminished elimination of acid from the blood, or through a decreased elimination of acid through other channels, in particular of carbon dioxide through the lung. Secondarily perhaps the elimination of acid through the glands of the skin, intestines may also play a part.

In the opposite way also an alkalosis may be produced in the blood; but in general any change tending to alter the hydrogen ion concentration of the blood cells calls forth counter-reactions which tend to neutralize the primary changes. Thus various possibilities of compensation exist which have been analyzed only in the last few

years, in particular by Yandell Henderson and Haggard and by Van Slyke.

The differentiation between compensated and uncompensated acidosis means an advance in our understanding of the changes in the blood; but it appears that this analysis will have to be extended in still another direction. So far almost exclusively the changes which take place in the hydrogen ion concentration and in the buffer system of the blood have been considered; this is sufficient, as far as certain functions, like the mechanism of respiration, are concerned; but it is insufficient in other respects, especially when problems of edema are considered. In this case we want to know whether or not the changes in the tissues take a course parallel to those in the blood. Now the compensatory changes in the blood may take place in either of two ways: (1) The excess of acid or alkali may be removed from the blood through excretion into the urine, into the air of the lung, or into the intestines. In this case the acid is practically eliminated from the body; or, (2) the excess of acid or alkali may be transferred to either blood cells or tissues. Compensation is accomplished in both cases equally as far as the blood is concerned; but as far as the condition of the tissues and the organism as a whole is concerned, there is a difference. In the latter case the hydrogen ion concentration of the blood may have become normal, while the hydrogen ion concentration of the organism as a whole remains unchanged and in the hydrogen ion compensation in certain tissues or cells, even an actual decompensation may have taken place at a time when compensation is accomplished in the blood and both effects may be the consequences of the same mechanism. It might therefore be advisable not only to distinguish between compensated and uncompensated acidosis, but also to distinguish between compensation through elimination and compensation through shifting of acid or alkali within the organism.

However, at the present time our knowledge as to the hydrogen ion concentration outside the blood is very fragmentary. We know through the determinations of Michaelis, Schade, Neukirch and Halpert and others that the hydrogen ion concentration in the muscle is slightly greater than in the blood, and that during work it may in this tissue change even to the acid side, and that the connective tissue juice has a hydrogen ion concentration which is above that of

the blood, although it is still on the alkaline side. We may assume that directly around the active cells and tissues the hydrogen ion concentration is somewhat greater than in the blood and that it decreases with increasing distance from the tissues, as a result of the diffusion of the acid products. Inasmuch as the content in non-diffusible ions differs in the blood and in the interstitial fluid, there will be presumably a slight increase in the concentration of hydroxyl ions outside of the vessels; this would tend to counteract to some extent the greater concentration of carbon dioxide and perhaps of other acid products outside the vessels.

As far as our analysis of edema is concerned, it is of importance that the reaction in the blood, as well as in the interstitial fluid, is still on the alkaline side and that accordingly the proteins as far as they are combined are not acid protein salts but alkali protein salts; furthermore, that the actual changes in hydrogen ion concentration, which have been found in non-inflammatory body fluids, are very small and do not, as far as we know, suffice to make the body fluids acid in conditions which lead most frequently to edema. The changes in potential or actual hydrogen ion concentration, in conditions which may lead to edema, have been studied in decompensated heart disease and in nephritis and we must therefore consider the principal results obtained in these diseases.

In cases of cardiac decompensation the arterial blood (Harrop) as well as the venous blood (Lundsgaard) may show unsaturation with oxygen. This is partly due to insufficient oxygenation of the blood in the lungs and partly to the slow circulation of the blood in the capillaries which leads to a more complete absorption of the oxygen from the blood. Yet this deficiency in oxygenation may be compensated for by an increased respiratory minute volume and in consequence of this compensatory process the oxygen consumption per unit of body surface may even exceed that found in normal individuals and the respiratory quotient may be normal (Peabody, Wentworth and Barker). In cardiac decompensation the most marked change which may affect the acid-base equilibrium in the blood consists in a relative retention of carbon dioxide in the blood associated with a low carbon dioxide content of the alveolar air. Therefore the carbon dioxide tension in the alveolar air is low in proportion to the

carbon dioxide tension in the arterial and venous blood (Peters and Barr). According to the last named authors the carbon dioxide tension in the alveolar air is lower than normal as compared with the plasma bicarbonate in cardiac decompensation and in dyspnea; in these cases the efficiency of the lung as a means for the oxygenation of the blood and the elimination of carbon dioxide is greatly reduced. In addition the slowing of the capillary circulation may also play some part as stated.

While there is thus a relative increase in carbon dioxide tension in the blood, the absolute values usually fall within the normal range. It is not always possible to determine how in these cases an uncompensated acidosis due to a relative surplus of carbon dioxide in the blood does occur, because certain individual differences, which are constant in a given person, seem to exist in the carbon dioxide : plasma bicarbonate ratio. A condition which would represent an uncompensated acidosis in one individual, might fall within the normal range in another. However, in some cases such an uncompensated acidosis does occur. In addition in some patients an absolute deficit in the blood alkali was observed; this again led in certain cases to an unpensated acidosis owing to lack of sensibility in the respiratory center.

The conditions found in cardiac decompensation seem to differ from those observed by Means, Bock and Woodwell in pneumonia, where, according to these authors, there exists an acidosis due to retention of carbon dioxide unaccompanied by a lowering of the alkali reserve. We may thus conclude that in cardiac decompensation the hydrogen ion concentration in the blood is in most cases either within the normal range or only slightly above this range. It is not conceivable that this change in pH can alter the colloids in the tissue spaces in such a way that edema follows. We shall return to this point in the next chapter.

In nephritis determinations of the alkali reserve by various investigators have shown a diminution in many cases (von Hoesslin, Sellards, Goto, Peabody, Meyers). Especially in cases of uremia the decrease in the blood alkali was marked. Rieger and Freund measured the amount of hydrochloric acid necessary to cause hemolysis in the blood of nephritics. They found this amount diminished in all cases of nephropathy accompanied by tubular and glomerular lesions; in

these cases there was no rise in blood pressure but a tendency towards retention of sodium chloride and towards the development of edema. They concluded that in these patients a diminution in the blood alkali occurs at a very early date. In cases of vascular nephropathy, on the other hand, where the blood pressure is high, with or without nitrogen retention and without a tendency to edema, there is no diminution in alkali reserve.

In dogs which had been poisoned with uranium nitrate or in which the uereter had been occluded, Elmendorf noted a diminution in the blood alkali and similarly McNider found in dogs affected by spontaneous nephropathy, or in cases of uranium poisoning, either a decrease in the blood alkali or at least a diminished power to reëstablish the normal alkali reserve after injection of an acid or a base into the animal, or after chloroform anesthesia.

According to McNider there exists a certain parallelism between the degree of diminution in the blood alkali and the severity of the pathological changes observed in the kidney in experimental nephritis. He furthermore found that injection of sodium bicarbonate may diminish the pathological effects of uranium poisoning in rabbits or of chloroform anesthesia in nephropathic dogs. This would indicate an etiological relationship between the diminution in the blood alkali and the development of kidney lesions. On the other hand, according to Karsner, Reimann and Brooks, the diminution in alkali reserve does not precede the kidney lesions. It had also previously been maintained by von Hoesslin and M. H. Fischer that the administration of sodium bicarbonate tends to decrease the albuminuria and to diminish the kidney lesions. However, while in some cases the administration of alkali may perhaps act favorably, on the whole clinical experience does not tend to substantiate the conclusion that sodium bicarbonate is particularly efficient in the treatment of nephritis. However, we shall refer below to some facts which indicate that in certain cases administration of alkali may be of some benefit in nephritis.

As to the causes of this diminution in blood alkali in cases of nephritis, the evidence points strongly to the conclusion that the kidney lesion is the primary factor which secondarily leads to a retention of acid in the blood. Greenwald has shown that in cases

of diminished alkali reserve in nephritis there is an increase in the inorganic phosphorus in the blood. Mariott and Howland found that this increase is due to the retention of acid phosphate and that the retention is caused by the inability of the diseased kidney to excrete this substance properly. These findings were confirmed by Feigl as well as by Denis and Minot. The latter found in 65 per cent of cases of nephritis a retention of inorganic phosphorus in the blood plasma, which becomes especially pronounced in cases which end fatally.

While usually in cases of increased acid production ammonia is formed in excess in order to neutralize the surplus of acid, in the alkali depletion found in nephritis such an excess of ammonia is lacking. The recent investigation of Nash and Benedict may perhaps explain this difference in the behavior of ammonia in various conditions in which a diminution in blood alkali is found. These authors have made it seem probable that ammonia is produced as a result of the activity of the kidney tissue. Perhaps the diseased kidney has lost entirely, or in part, the power to produce ammonia and thus the difference between nephritic diminution in blood alkali and the corresponding change in other conditions may be explained. The results of Mariott and Howland suggest that the retention of acid phosphate is the cause of the alkali diminution in nephritis, and thus the actual or potential acidosis would be rather the result than the cause of the nephritis. While this conclusion is probably essentially correct, still the acidosis as such may perhaps contribute to the inability of the kidney to excrete sufficiently the acid produced and in this way a vicious circle may be established.

The findings of Straub are also confirmatory of the view that the disturbed renal function leads to alterations in the composition of the blood, and at the same time support the suggestion made above as to the function of alkali. He finds that while the normal kidney is able to regulate the elimination of acid and alkali taken up with the food in such a manner that the hydrogen ion concentration of the blood remains constant, the diseased kidney is no longer able to excrete a surplus of acid or it can accomplish such an elimination only if at the same time alkali is given. Straub finds likewise a great variability in the anions present in the serum of nephritic individuals

in contradistinction to the constant composition of the normal serum. The character of the anions present in such cases depends to some extent upon the anions taken in with the food. Nephritic patients have lost the power of keeping constant, through excretion, the constitution of the blood in inorganic ions. It is therefore possible that other anions besides the phosphates are implicated in the retention of acid in the blood.

The evidence which we have presented so far, and similar observations by Means and Rogers, as well as by Barr and Peters, prove conclusively that the diminution in the alkali of the blood is an early result in nephritis; furthermore the origin of this diminution has been established. However, these investigations do not give us any information as to the actual hydrogen ion concentration of the blood and from our point of view the question, whether this concentration is increased in nephritis, is perhaps the most important one. The diminution in blood alkali due to the retention of non-volatile acids might be compensated for either by the movement of alkali from tissues to the blood, or by a diminution in the carbon dioxide tension of the blood. Recent investigations show that such a compensation frequently occurs. Thus Peters, Barr and Rule found in a case of chronic nephritis with hypertension the alkali value of the blood at the lowest value of the normal range; yet the hydrogen ion concentration of the blood was normal. H. Straub in an extensive study has recently shown that in many cases of renal disease the hydrogen ion concentration of the blood remains unchanged, although the carbon dioxide binding power of the blood is diminished; in such cases compensation was accomplished through an increased elimination of carbon dioxide in the lung. In other cases, however, there is according to Straub an increase in hydrogen ion concentration, but—and this is important from our point of view—without a corresponding tendency towards the development of edema in such individuals. Means, Bock and Woodwell likewise observed a nephritic patient with low blood alkali and decompensated acidosis. The evidence thus far at hand points then to the conclusion that no definite relation exists between an increase in the hydrogen ion concentration of the blood in heart and kidney disease and edema. In the following chapter we shall find further evidence sustaining this conclusion.

XVII. THE LOCALIZATION OF EDEMA AND ITS BEARING ON THEORIES OF EDEMA

Within the last decade a conception of edema has been the subject of much discussion, which differs from previous theories in that it assumes that the seat of edema is not, as had been previously believed, mainly the interstices of the connective tissue, the lymph spaces and the serous cavities, but rather the cells and parenchyma of the various organs. This theory furthermore assumes that the cause of edema is not, as had hitherto been conceived, a change in the condition of the walls of the blood and lymph vessels, nor an alteration in the mechanics of the circulation, nor is it a change in the physio-chemical relation between the fluid in the blood and lymph vessels on the one hand, and the fluid in the surrounding interstitial spaces and in the serous cavities on the other hand, but that the cause of edema is an alteration in the physico-chemical relation between the circulating fluid and the parenchyma of the organs. It is furthermore assumed that this alteration is due to a pathological condition in the metabolism of the parenchyma. Following an injury chemical changes are supposed to occur in the cells or parenchymatous tissue in general, as a result of which water is drawn to the organs from the surrounding circulating fluid. Lazarus-Barlow as early as 1895 expressed the view that anemia in the tissues is responsible for edema following circulatory disturbances. He believed that under this abnormal condition the tissues needed an increased amount of fluid and that the resulting edema represented thus an adaptive process, comparable in that respect to inflammation, which likewise has the characteristics of an adaptive process. Edema was said to bring about a dilution and elimination of the injurious waste products of metabolism. In this connection we may mention that a somewhat similar effect has been attributed to edema by more recent authors who, like Widal, have pointed out that edema and uremia are to some extent mutually exclusive and who attributed thus to edema a certain detoxicating function. In a similar manner Lazarus-Barlow explained edema of the lung as well as inflammatory edema; renal edema also he attributed partly to the retention of waste products in the tissues.

While teleological viewpoints were prominent in the conceptions of Lazarus-Barlow, the parenchymatous theory of edema, free from such considerations and based merely on physio-chemical findings, was first expressed by Jacques Loeb in 1898. This author found that excised frog muscle could be made to take up an increased amount of water if acid or alkali was added to the solution of sodium chloride into which the muscle had been immersed. He assumed that the acid caused an increase in osmotic pressure in the muscle and thus led to edema. Subsequently he applied these observations and conclusions to edema in general. According to his view edema is found under various conditions of cell or organ injury, which have all in common an interference with the processes of oxidation. In consequence of these interferences acid is produced in the cells, and this leads to physico-chemical changes within the cells or tissues and especially to an increase in osmotic pressure. Edema is the result of these changes. Even pulmonary edema he supposed to be due to this mechanism. All edema can be exemplified in the swelling which takes place in a ligated frog leg immersed in water below the place of ligation. Here the tissues take up water as the result of the production of acid, which, in conformity with the conclusions of Araki, is called forth by the lack of oxygen. Jacques Loeb considered the state of the cell colloids as an important factor in determining the amount of water attracted by the cells. He showed that potassium salts cause a greater swelling of muscle than sodium salts and he compared this effect with the affinity of potassium soaps for water.

However, this author very soon reached the conclusion that this theory of edema was not in harmony with a number of important facts and he therefore abandoned these conceptions, the hypothetical character of which he had recognized from the beginning. Very similar ideas were soon afterwards expressed by Martin H. Fischer who attempted to substantiate them in a series of experiments dealing mainly with the affinity of colloids for water; in fact in contradistinction to his predecessor, he emphasized the rôle of organ colloids, the swelling of which under the influence of acid he considered as the main source of edema. Fischer also bases his theory largely on experiments with the frog leg and adopts the conception that lack of oxygen, leading to acid formation within the cells or

tissues, is the initiating factor in edema. He likewise explains pulmonary edema on this basis. He differs, however, in one important respect from the views of Jacques Loeb. While the latter assumed that the production of acid leads to an increase of osmotic pressure within the cell or organ parenchyma in general, Fischer believes that the acid acts on the cell colloids and increases their affinity for water in a manner similar to that of gelatin or fibrin, a conclusion in harmony with the experiments of Spiro, and others, who have shown that acid can cause a swelling of these proteins.

Alkali, pyridin, urea, amins and similar substances may likewise increase the affinity of colloids for water, but in actual edema, acid formation in the organs is the essential cause of the edematous swelling. Edema is then essentially a problem of the hydration of cell colloids; and the production of acids, through lack of oxidation, is the main cause of this increased hydration. Other substances may perhaps occasionally come into play, but they are, to say the least, of minor significance. All varieties of edema, wherever it is situated, whatever its apparent clinical origin, are to be explained in a similar manner. This applies equally to cardiac, renal and pulmonary edema; it also applies to edema of the brain, to inflammatory edema and toxic or anemic edema. It furthermore applies to glaucoma which, according to Fischer, consists in a swelling of the colloids of the eye. Any condition that causes swelling of gelatin or fibrin or of the frog-leg, when it is deprived of its circulation, may cause edema; and similar conditions in the eye cause glaucoma.

Edema of the serous cavities, or of the interstitial connective tissue is merely due to secondary changes, which are comparable to alterations observed in colloids in the gel state; they may gradually retract and during this process press out water (syneresis); the water, thus set free through secondary changes in the primarily edematous organs, accumulates in the serous cavities and this process causes ascites, hydrothorax and hydropericardium.

The swelling caused in colloids through acid or alkali can be counteracted by the addition of various neutral salts, and this dehydrating effect of salts shows a gradation similar to that previously found by Hofmeister, varying in accordance with the effectiveness of the ions constituting the salts. Citrates, tartrates, acetates, phosphates and

sulphates gave an especially marked dehydrating effect on colloids and are therefore according to Fischer most effective in the treatment of edema. But all neutral salts, especially in hypertonic solutions, have this effect and may therefore be recommended in the treatment of edema; dehydrating salts in particular may benefit glaucoma, if injected under the conjunctiva. In addition administration of an alkali is to be recommended in order to neutralize the acid, which this author believes to be responsible for the swelling of organ colloids.

The main difference between the earlier conceptions and those of M. H. Fischer concerns the character of living cells and the exchange of substances between the latter and the surrounding fluid. While Jacques Loeb assumed that cells are surrounded by a protoplasmic membrane which possesses a selective permeability, Fischer on the contrary denies the existence of such a limiting membrane and believes that the cell colloids are immersed directly in the body fluids and are therefore subject to the same laws of swelling as gelatin and fibrin.

Various objections can be raised to these conceptions of edema, and we shall briefly discuss the principal ones:

1. The seat of edema is primarily not the parenchyma of organs but the interstitial tissue. All direct observations point to this conclusion which has again been maintained more recently by pathologists like Marchand, Klemensiewicz, Lubarsch and others. Hülse, who, like Fischer, believes that the cells and parenchyma in general are primarily affected, does not give definite facts in support of his contention.

In the case of acute pulmonary edema in rabbits, produced through the intravenous injections of adrenalin, it can be clearly shown that fluid is pressed out from the blood-vessels into the interstitial spaces and alveoli of the lung. The conditions under which this occurs are not compatible with the assumption that the edema is due to changes in cells or even in connective tissue fibrils composing the lung tissue which would lead to an attraction of water. Moreover in edema of the skin the spaces between the connective tissue fibrils are primarily affected and not the fibrils as such. In experimental edema, produced in rabbits through the intravenous injection of a solution of sodium chloride, the edema originates in the serous cavities and in the in-

terstitial spaces of the connective tissue around the pancreas and salivary glands, and not in the parenchyma of organs. These and other observations make impossible the interpretation of these edemas as comparable to the pressing out of water from gels (so called syneresis). The edematous condition of the cells proper and of the parenchyma in general is usually a secondary phenomenon.

As we have mentioned above, in certain cases fibrillar structures as well as cells may become edematous. This applies also to the hydremic plethora, produced experimentally in rabbits, where for instance, the secreting cells of the salivary glands may take up fluid (Wertheimer and Battez); we have every reason for believing that this is a process secondary to the interstitial edema, which is more marked than that of the tissue constituents. The abnormal environment in which the cells are placed, as the result of the interstitial edema, and the movement of an abnormal fluid through the gland proper into the gland ducts are probably responsible for an injury of the cells and the subsequent imbibition of fluid. This condition is perhaps comparable to changes in red blood corpuscles which have been observed by Prigge after intravenous injection of an hypertonic solution of sodium chloride into patients suffering from pneumonia. He finds that while usually after such an injection fluid is given off by the corpuscles to the surrounding medium in accordance with the laws of osmosis, sometimes the reverse process may occur and the injured corpuscles may take up fluid from the blood. Thus an edema of the erythrocytes may occur which is secondary to the hydremic condition of the surrounding medium.

2. There is no reason for assuming that the formation of acid in the tissues is the essential cause of edema. We have already considered in the preceding chapter the formation of acid in conditions leading to edema, and concluded that while there may be an increase in the hydrogen ion concentration in the circulating blood in certain cases of cardiac decompensation and in kidney lesions, it is slight and no parallelism is apparent between this increase in hydrogen ion concentration and the development of edema.

We shall now discuss under what conditions the production of acid in the body might lead to the formation of edema. We must distinguish between acid production in the circulating body fluids

(blood and lymph) and that in the interstitial fluid, which is temporarily held in the spaces surrounding the various cells and tissues. In the former there are present two factors which tend to antagonize the effect of an increase in the concentration of acids, namely, special buffer substances and salts in general. The buffer mechanisms tend to oppose the deviation in the ratio of the fluid towards the acid and alkali side and would make necessary the addition of considerably greater amounts of acid and alkali in the living organism than in the in vitro experiments. This point has been especially emphasized by Lawrence Henderson and E. J. Cohn and by Bayliss. As to the second factor, the neutral salts present in the body would tend to oppose the acid and alkali effect of proteins, as has been pointed out by A. R. Moore. But even if at last these mechanisms have been overcome, then another factor would come into play which in the living organism would prevent the production of edema under the influence of acid. In the circulating body fluids a certain proportion of the proteins are in all probability present as alkali-proteinates. As such they would tend to bind a certain amount of water. Now, if free acid came in contact with these substances, the acid would first convert some of the alkali proteinates into isoelectric proteins. Instead of increasing the water binding power of the proteins, this process, on the contrary, would decrease it. The addition of considerably greater quantities of acid would be required in order to produce a conversion of the isoelectric protein into protein-acid combinations, in which the protein would be the kation and the anion of the acid molecule the anion. Under these conditions the water binding power might reach again its original level and might gradually surpass it.

But is is not conceivable that the slight alterations in hydrogen ion concentration, which have been observed in the blood plasma, would be sufficient to bring about so far going changes and it is doubtful if such changes would be compatible with the necessary functions of respiration and tissue metabolism.

As far as the interstitial fluid is concerned, we have reason for assuming that the hydrogen ion concentration is here slightly higher than in the circulating body fluid; but a constant exchange of substances between these two kinds of fluids would tend, even in the tissue fluid, to keep changes in hydrogen ion concentration within

very narrow limits and the proteins would presumably still remain slightly on the alkaline side. Likewise in the tissue spaces buffer substances and salts again would tend to counteract an acid effect on proteins. The conditions present in the tissue fluids would therefore in principle be similar to those obtaining in the blood and lymph.

As far as the cells are concerned, which are surrounded by the interstitial fluid, we have shown that a slightly acid reaction in their environment may, under certain conditions, not only not lead to edema of the cells, but on the contrary tend to increase the consistency of the cells and thus to prevent the entrance of water into the parenchyma proper; in this way acid may in some cases promote rather than diminish certain cell activities.

That thus in the interstitial tissue acid cannot be the cause of edema in the majority of cases, is also proven by the hydrogen ion concentration of edematous fluids which have been found not to differ much from that of the blood. Even in the inflammatory edema produced through the instillation of mustard oil into the conjunctival sac in rabbits, Hirschfelder found the reaction of the edematous fluid to correspond to a pH of 7.2 to 7.5 which is close to the alkalinity of the venous blood. Schade likewise finds the hydrogen ion concentration of edematous fluid similar to that of the blood. It is however possible, as Schade points out, that in certain inflammatory processes acid may be produced in somewhat larger quantity, and this may perhaps increase the intensity of an edema which was primarily caused by other factors.

Only if a large amount of cellular material were breaking down very rapidly, such as occurs in the case of purulent inflammation, could enough acid be produced to become possibly a factor in the production of a localized edema, but this would constitute an extreme and strictly localized condition which would not be of significance as far as the analysis of edema in general is concerned.

Thus theoretical considerations and the actual determination of the hydrogen ion concentration lead both to the same conclusion; but in addition experimental and clinical facts give to it additional support. We may briefly mention some of these observations: (*a*) In experiments in which he produced edema in Trendelenburg preparations of frogs, through perfusion of salt solutions, Gayda found that

the addition of alkali to the perfusion fluid did not prevent the occurrence of edema. (*b*) The oral administration of considerable amounts of acid and alkali extending over a longer period of time, which according to Henriques and Ege may change the hydrogen ion concentration of the body fluids within relatively wide ranges, does not seem to lead to the production of edema. (*c*) In diabetes where the hydrogen ion concentration changes towards the acid side to a much greater extent than in many cases of renal or cardiac affections, which latter are often followed by edema, an edematous condition does not usually occur. On the contrary; diabetic individuals very often show a deficit of water, a condition which has been attributed by some authors to the increase of sugar in the blood of these patients. It is, however, possible to produce in diabetes, as well as in cases of inanition, extensive edemas through the injection of large quantities of sodium bicarbonate solutions. These edemas are possibly due to the introduction not of the hydroxyl but of the sodium ions and would thus be another instance of the effect of sodium chloride in the production of edema. We have discussed this kind of edema in a preceding chapter. (*d*) It has been shown by Schade that acid causes a swelling of the connective tissue fibrils, while alkali on the contrary causes a swelling of the colloidal material, which is supposed to fill the interfibrillar spaces. Now in typical cases of edema, the interfibrillar spaces are the seat of the swelling rather than the fibrils proper. This would be in agreement with the slightly alkaline character of the body fluids, which would become still further removed from the isoelectric point through the addition of alkali and consequently would bind a larger quantity of water. It must, however, be conceded that there is no certainty as to the existence of an amorphous colloidal ground substance, filling the interfibrillar spaces, which Schade and others assume. The presence of such a substance in a somewhat modified form is also assumed by Laguesse. This author maintains that the loose connective tissue consists of a system of lamellae formed by colloidal material in which are embedded the connective tissue fibrils. Connective tissue cells line these lamellar structures and these cells are also found in the interior of the lamellae. The latter can glide over each other. According to Laguesse these interlamellar spaces may serve as water reservoirs, if an excess of

fluid is eliminated from the vessels. In addition an imbibition of the colloidal ground substance would occur in edema. On the other hand Nageotte maintains that the lamellae of Laguesse are merely systems of fibrillar nets in which the fibrillae are closely approximated to each other. Spaces which intercommunicate with each other separate the fibrillae in case of edema. A homogeneous gelatinous substance, in which the fibrils are embedded, does not therefore exist, according to Nageotte. It is very probable that the latter view is the correct one and that in edema the fluid, with which is mixed a certain amount of colloidal protein material, separates these fibrils. (*e*) According to Bauer, acid instead of causing a swelling of nerve substance, on the contrary produces a dehydration of this tissue and acid cannot therefore be the cause of edema of the brain substance proper. (*f*) There are apparently some conditions where lack of oxidation processes and subsequently acid production or direct formation of acid may lead to localized edema within the cells of certain organs. Such changes have been described by Martin, Loevenhart and Bunting in tissues exposed to oxygen deficiency and by E. A. Graham in the liver of dogs under the influence of chloroform poisoning. Now, from our point of view it is of interest that in these cases a typical edematous condition of the interstitial tissue did not develop. (*g*) According to Fischer inflammatory edema depends upon the absorption of water by the colloids of the tissue which has been injured through the inflammatory alteration. Contrary to this view, Hirschfelder has shown that the conjunctivitis and chemosis of the lid which usually follow the instillation of mustard oil into the conjunctival sac of the rabbit, do not occur, if the lid is excised within three to four minutes following the instillation, at a time when the edema has not yet begun to develop. If the lid is next placed in Ringer's solution or in rabbit serum, it does not become edematous. Hirschfelder concludes therefore that the circulation is necessary for the development of this edema, but the circulation does take place through vessels in which the state of contraction and the permeability have been altered. (*h*) As Wallace and Pellini have pointed out, a number of substances which produce functional or structural changes in the blood-vessels call forth at the same time a state of acidosis. Now, from our point of view it is important that no relation

exists between this acidosis and the edema producing power of these substances.

3. M. H. Fischer assumes that, as far as their permeability for water and dissolved substances is concerned, cells and tissues are comparable to pieces of gelatin or fibrin; this author denies therefore that there exists a protoplasmic cell membrane, with a distinctive physico-chemical behavior and function and with a permeability for water and salts which may differ from that of the colloids which make up the contents of the cells. Contrary to this view, the studies of many investigators, like Hoeber, Jacques Loeb, Bethe, R. S. Lillie, Osterhout and others, have brought to light many facts which can hardly be explained otherwise than by the conclusion that a distinctive protoplasmic cell membrane separates cells and surrounding tissue fluid. The recent studies of Embden and his collaborators furnish additional evidence in favor of the existence around muscle of a protoplasmic membrane, possessing a distinctive permeability, which varies under different conditions.

4. One of the most important facts in the interpretation of certain experimental edemas is the rôle which sodium chloride retention plays in determining the intensity and duration of the edema. As we have seen, all evidence points to the conclusion that it is the sodium rather than the chlorine ion which is responsible for this effect and that other kations do not have an effect comparable to sodium. On the contrary the administration of potassium and calcium may lead to the elimination of the edematous fluid. This specific effect of sodium is not restricted to edema of renal origin, but may appear in other kinds of edema as well, and a theory of edema can therefore not disregard the connection between salts and edema.

Now it is important to note that the effects of sodium chloride in edema do not show any parallelism with the action of this salt on proteins; sodium chloride tends to diminish the swelling of gelatin under the influence of acid and alkali, while it increases the intensity of edema, or may cause edema as we have seen above. On the strength of the action of this salt on proteins, M. H. Fischer recommends hypertonic solutions of sodium chloride in the treatment of edema and particularly of glaucoma. The results of this mode of treatment do not seem to have been generally favorable, and when hypertonic salt

solutions have a beneficial effect on localized edema, it is due to their osmotic action and not to their effect in counteracting the influence of acid and alkali on proteins; otherwise isotonic solutions of this salt should prove effective in the treatment of edema; but this is not the case. In particular, this mode of treatment has not been found successful in glaucoma, according to the experience of the majority of ophthalmologists. Such a result was to be expected, if we consider that glaucoma is not due to an increased hydration of the tissues constituting the eyeball; and even if this were so, it would be difficult to understand why the relatively very small quantities of hypertonic salt solution, recommended by Fischer in the treatment of glaucoma, should be able to overcome successfully the affinity for water on the part of the colloids of the eye. The same discrepancy between the effects of salts in edema and their effect if acting directly on colloids was observed by Heubner in his study of the action of salts on the ligamentum nuchae in cattle. Quite recently Fischer offered a new explanation of the effects of sodium salts in edema in which he concedes the effect of this salt in increasing edema; but again his explanation is based on the assumption that edema consists primarily and essentially of an entrance of water into the parenchyma of organs and that the water is therefore mainly intracellular in character; for this and other reasons his hypothesis is not convincing.

As to the different degrees of effectiveness in the dehydrating action of various salts on colloids, we have in a preceding chapter referred to investigations showing that the citrate, tartrate, phosphate and acetate ions, which, according to Hofmeister and Fischer, exert a specific dehydrating effect on proteins, influence primarily the hydrogen ion concentration of the solutions and that therefore a specificity in the action of these ions does not really exist.

W. Hülse who, like Fischer, assumes that the primary seat of edema is the parenchyma of organs, recognizes the difficulties attaching to the hypothesis which attributes to the effect of acids the major rôle in the development of edema, and he therefore states that salts or other molecules combining with the colloids, cause their hydration. This author however gives no definite facts in support of his contention and he does not thereby account for the difference in the action of sodium and potassium salts in edema.

If we take into consideration all these facts, we may conclude that there is no reason to accept the view that edema consists in a hydration of the colloids in the parenchyma of organs caused by the influence of acids.

XVIII. THE MAIN FACTORS IN THE DEVELOPMENT OF EDEMA

In this concluding chapter we shall recapitulate some of the more general points of view we have arrived at, and we shall consider the relative importance of the various factors which we have discussed in the previous chapters. Such a discussion must necessarily be of a tentative character and it will at the same time serve to show the defects in our knowledge and the apparent or real contradictions in certain of the observations, clinical and experimental, and in some of the conclusions arrived at by different investigators.

The problem of edema

The factors which regulate the exchange of fluid and dissolved substances between blood and lymph vessels on the one hand, and the surrounding tissue spaces and serous cavities on the other, and again between the latter and the organs are complex and to this complexity corresponds the complexity of the factors which lead to a disturbance of this mechanism. While heretofore it has been customary to consider edema as a chapter in the pathology of lymph formation, we have considered it in a more general way as an interference with the mechanism which regulates the distribution of water and of dissolved substances in so far as the latter influence the distribution of water in the organism, and in particular as an interference with the mechanism which tends to keep in the first place the constitution of the blood and secondarily also the fluid of the tissue spaces constant. These interfering factors may be of a general or of a local character.

A complete understanding of edema would therefore presuppose a complete analysis of the factors which determine the normal movements of fluid and dissolved substances, also of the forces which regulate the absorption of fluid in the intestines, its excretion through kidney and elsewhere, and which regulate the permeability of capillaries and the constituent elements of organs. We would have to

know the influence of the mechanical factors concerned in the pumping of blood through the vessels on the movement of water outside the vessels, as well as the influence of various substances originating in the body on this movement. At present we can only indicate where a deviation from the normal factors sets in. Our main difficulty concerns the sequences to these initial disturbances. These we understand as yet only incompletely.

Correlated movements of fluid

We have seen that there is reason for the conclusion that under normal conditions the principal factors which determine the movement of water and dissolved substances and which regulate this mechanism form one connected whole, in which a disturbance in one part causes a regulatory disturbance at another point of the mechanism. Likewise in general edema similar connected mechanisms come into play, inasmuch as, for instance, an interference with the elimination of fluid and dissolved substances may cause changes throughout the body and lead to an overflow into the tissue spaces, while conversely this condition is remedied as soon as the primary disturbing factor is removed. We have found a number of instances in which not only this connection between different parts of the mechanism was clearly recognizable, but in which moreover the forces at work could be determined. Thus it was quite evident that the effect of adrenalin on elimination of fluid through the kidney influenced absorption from the peritoneal cavity, and that osmotic and diffusion potentials transmitted the effect from one part of the body to another part. In a similar manner, if under the influence of caffeine more water and salt pass from the blood into the kidney, the movement of these substances is correspondingly influenced throughout the organism at various points of the circuit. When we cause a deficiency or an excess in the intake or elimination of sodium chloride, a correlated movement of salt and water from tissue to blood, kidney or in the opposite direction follows. In the experiments of Magnus the excess of salt caused by the intravenous injection of a solution of sodium chloride is temporarily stored in the tissues and then given off by tissues to blood and kidney. Osmotic and diffusion differentials apparently regulate this movement. The amount of water and sodium

chloride deposited in the tissues has a marked effect on the elimination of water and salt through the kidney. There is a correlation of the exchange of fluid between tissue and blood on the one hand, and between blood and kidney on the other hand. The blood represents a station of transit, which is usually only temporarily disturbed, because it possesses outlets in both directions and thus a compensation can be more readily brought about. Under pathological conditions the amount of sodium chloride and water may vary also in the blood; during the period of discharge of the edematous fluid the concentration of sodium chloride in the blood may be temporarily increased. If diuresis takes place in cardiac edema, a dilution of the blood occurs at first and subsequently an increased concentration. In case of edema we find the movement of water changed in both directions in a correlated manner; while there is an inhibition of the movement from the tissues to the blood. In nephritis the drinking of much water may lead to an excess elimination of water into the tissues owing to the insufficient elimination through the kidney, and this is perhaps correlated with changes at the tissue-blood-vessel border. We have reason for assuming that this connected movement depends to a great extent on osmotic and diffusion potentials which may be, as the experiments of Priestly suggest, so small that they represent osmotic and diffusion differentials, and if we consider the changes in the permeability of blood-vessels which evidently occur in response to primary alterations in blood and tissues, there is reason for assuming that these changes also may play a part in this correlation.

Excess and pendulum reactions

This interconnection of mechanisms may lead to excess or pendulum reactions: a temporary excess of substances in one part of the interconnected system is created, which is equilibrized soon afterwards. Two such pendulum phases may even occur in succession. Thus in nephritis the drinking of much water may lead to an excess elimination into the tissue and to a temporary increased concentration of the blood. If in cases of acute glomerulonephritis or hunger edema at the time of the discharge of the edematous fluid a surplus of sodium chloride is taken in, more sodium chloride may be excreted than has been added to the diet. The addition of sodium chloride may mo-

bilize the stored up salt, which evidently is very loosely bound to the tissues. In cases of cardiac decompensation, after a dry retention of sodium chloride has taken place, an excess of the salt may be given off. In a similar manner drinking of water may cause an excess diuresis, more water being eliminated than had previously been taken up, if the water had been stored in the body without a proportionate amount of sodium chloride having been retained. Thus during the discharge of the edematous fluid an excess elimination of water may occur and this may lead to a temporary inspissation of the blood.

We find then, for instance, in hunger or renal edema, during the time of the discharge of the edematous fluid a process taking place similar to that seen under normal conditions, where drinking of water tends to mobilize a mechanism, which leads to a movement of water from blood or tissue to kidney, and which more than compensates for the intake. In edema this occurs as soon as the primary disturbance has been removed and the mechanism has been released which permits water and sodium chloride to move from tissue to blood or kidney.

Such excess reactions may also take place in cases of pre-edema when the mechanism of water and salt movements is not yet fully disturbed; here copious water drinking may set to work the opposite mechanism leading to an excess elimination of water through the kidney. The fact that such mechanisms exist not only in renal edema but also in hunger edema, when apparently the kidney functions well, suggests that there are mechanisms which regulate the movement of sodium chloride and water from the blood to the tissue and vice versa, independently of the kidney function and that the reëstablishment of the mechanism, which sets free the movement from tissue to blood, may stimulate the kidney to action, provided the renal function is satisfactory. A double regulatory mechanism thus exists: (1) A disturbance of one part of the connected mechanism leads to a compensatory reaction in the other part, and (2) A localized regulation, principally of a chemical, but secondarily also of a mechanical nature, occurs at the various boundaries.

We see then that the mechanism regulating the water and sodium chloride movement and content of the organism is a very delicate one; the lability of this mechanism is so great that a temporary excess

of water or salt in one part of the body may lead to a greater elimination of water and salt than the amount taken in and an excess reaction is brought about. Thus under certain conditions the movement of water and sodium chloride resembles reactions which take place under the influence of a stimulus, no simple quantitative proportion existing between stimulus and reaction. And this fact suggests the participation of sensitive tissues in these reactions, such as a variable permeability of capillary walls, which finely adjusts itself to various conditions.

Reversal of the movement of water and sodium chloride

In edema there are at work factors which change the current of water and sodium chloride in such a manner that a movement of these substances towards the tissue spaces and serous cavities is facilitated and the opposite movement from the tissue to blood and kidney is impeded. Such a change in the direction of the movement can be shown to exist in experimental uranium nitrate poisoning.

We have shown that such a reversal can be experimentally produced or accelerated through administration of caffeine in nephrectomized animals. A similar effect can be obtained in diabetes insipidus through administration of pituitrin. If this reversal continues for a sufficient length of time with sufficient energy, and if enough water is given, edematous or at least pre-edematous conditions can thus be experimentally produced. It is probable that osmotic and diffusion potentials are active in this reversal of current. Differences of concentration may perhaps be associated with changes in the permeability of membranes, which may lead to changes in the concentration of various substances on both sides of the membranes. We know that pituitrin may affect the permeability of membranes, decreasing the permeability of the capillaries.

The action of thyroid resembles the effects of pituitrin and caffeine in so far as all of these substances act on the intermediate water and sodium chloride movement; but while caffeine and pituitrin under the conditions we mentioned increase and accelerate the movement towards the tissues, thyroid accelerates the movement in the opposite direction. We see then that certain substances may affect the intermediate current of water and sodium chloride in a specific manner

leading either to a pre-edematous condition or to the opposite effect, the discharge of the edematous fluid. Whenever the normal current of water tending to excretion is interfered with, a reverse current towards the tissues tends to occur, similar to that accelerated by caffeine after extirpation of the kidney. Caffeine and similar substances, which under normal conditions hasten the elimination of sodium chloride and water, and in an edematous state may induce the discharge of the edematous fluid, provided the kidney is sufficient for this purpose, may otherwise not only be without effect, but may, as we have seen, even favor the opposite movement, namely, that towards the tissues.

There are some indications that the movement of sodium chloride in one direction may be equalized by a movement of other substances in other directions, and that thus an equalization in osmotic pressure may be brought about.

Edema as a compensatory process

Under various pathological conditions mechanisms exist which tend to keep the composition of the blood as constant as possible. It has, for instance, been shown that there is a mechanism which in this sense takes care of the hydrogen ion concentration of the blood, substances which threaten a marked alteration being soon eliminated. In this way the circulating medium, which keeps up the exchange of substances between the various parts of the organism, an exchange leading to the elimination of the waste products, is enabled to function at the expense of parts in the organism which are less essential for the organism as a whole. There is also a mechanism which keeps the water content and the concentration of various substances in the blood constant. Two main outlets exist for material which might lead to pathological alterations in the blood, namely, the tissues and the kidneys. There seem to be special reservoirs which, in the normal organism, principally take care of a surplus of water or sodium chloride, the muscle in the case of the former and the skin in the case of the latter. After a temporary storage, the surplus is eliminated chiefly through the kidney. If the disturbance connected with the retention of these substances is greater, they are eliminated mainly into the subcutaneous tissue and into the serous cavities and are kept there

until the disturbance in the primary mechanism, has been removed. Thus again the constitution of the circulating medium is kept constant, at least within certain limits, although we have seen that temporary alterations due to excess and pendulum movements do occur; and if the alteration is furthergoing, certain changes in the blood may be of even longer duration. But the surplus tends to be eliminated into the tissues and to be kept there and thus edema is produced. In this sense we may consider edema as a compensatory process insuring relative safety to the organism.

It is of interest to inquire, why the blood has this advantage? It seems to be due to the fact mentioned above that the blood is surrounded on both sides by a mechanism which serves for elimination of water and dissolved substances, namely, the tissues and the kidney. It is this advantageous position of being in the center of this system which tends to insure the relative constancy in the composition of of the blood. In addition to representing a place of elimination, the tissue also is a supply room, from which substances may be taken up. As we have seen, there is a multiplicity of primary factors which regulates this constancy in the distribution and movement of water and salt in the body. They are connected with each other and to some extent a deficiency at one point can be compensated for through the regulating activity of another part. A last regulation occurs in the form of edema. If we inquire into the factors which serve the function of these primary mechanisms, the evidence points to the conclusion that changes in the permeability of membranes, and in particular of the capillaries and osmotic and diffusion potentials, are the principal instruments which come into play in the normal regulation of the constitution of the blood, as well as under those conditions which lead to edema.

Edema as a graded process

According to the definition, edema is a swelling due to the collection of fluid in certain parts of the body; this definition of edema would presuppose a discontinuous process. In reality all transitions seem to exist between the normal distribution of fluid on the one hand, and edema on the other, a state of pre-edema representing an intermediate stage between these two extreme conditions. The determinations of

Kauffman in heart disease indicate the existence of such intermediate stages under circumstances which ultimately lead to cardiac edema. The transitional stages are due not only to a continuity in intensities in the accumulation of fluid, but also to variations in duration which range from temporary disturbances, as those of shock, to long continued edema.

Multiplicity of factors in edema

We can distinguish three sets of factors which regulate the normal movement of water and dissolved substances. (1) The primary factors represent, as we have seen, a more or less connected mechanism, which includes the absorption, circulation and elimination of fluid. (2) The secondary factors include diffusion and osmotic potentials and perhaps endelectrosmotic forces, changes in the permeability of membranes, and probably to a limited extent filtration pressure. (3) We can, if we proceed still further in our analysis, recognize a third class of factors, comprising the means through which the second set of factors exert their effect. These would include the distribution of sodium chloride and of proteins, both of which are of special importance in establishing and regulating osmotic and diffusion potentials; in addition the protein aggregates may retain water in a specific manner. The third class would also include those factors which regulate the permeability of membranes,—as for instance, a certain equilibrium of ions,—the action of certain hormones and other conditions. Now all of these factors which are of significance in the normal movement and distribuiton of fluid must necessarily also be factors in the development of edema; but there is discernible besides in a number of cases a multiplicity of those factors which deviate from the normal to such an extent that edema results. Some of the better known instances are the following: Hydremia as such does not cause general anasarca in the rabbit; but if in addition effects are added, which in all probability increase the permeability of the capillaries, as for instance, those following the administration of iodine or arsenic, and those following the death of the capillaries, then general edema follows. While venous obstruction alone may not cause edema in many cases, combined with hydremia or with arterial hyperemia, it may produce this effect. In a similar manner venous obstruction

accompanied by the injection of hypertonic salt solution may cause edema. Administration of amylnitrite may cause edema in chromate rabbits, and it may increase it in uranium nitrate nephritis; presumably this substance leads to a slowing of the circulation and thus to an increase in the permeability of the vessels. In the embryo, after elimination of the kidney function, injury to the vessels of the skin in the area surrounding the place of incision, causes edema to appear at this point, while elsewhere cutaneous edema is lacking.

There are indications that a similar multiplicity of factors comes into play in clinical forms of edema. Thus in edema observed in undernourishment several factors may be responsible, as an increased deposition of sodium chloride in the tissues, hydremic blood, and a consequent decrease in the power of the blood to retain and attract water, and perhaps an increased permeability of the vessels and a weakened circulation. In nephritis possibly the effect of substances given off by the diseased kidney, or of substances causing simultaneously pathological changes in kidney and blood-vessels, may be added to effects due to the retention of substances normally eliminated through the kidney, which latter may set up osmotic and diffusion potentials and influence the membrane permeability. In cardiac decompensation there is a slowing of the circulation which is associated with a dilatation and presumably an increased permeability of the capillary vessels; but an increased filtration pressure may perhaps exert an additional influence in certain cases. Similarly in lymphatic edema there may be added to the mechanical factors changes in the permeability of the vessels and in osmotic potentials. As we have seen multiple factors may even be present, when one factor seems to play a predominant rôle, as, for instance, in inflammatory edema, where the increase in the permeability of vessels is the most striking feature. In this case an increase in osmotic pressure and in the colloid content of the affected area may also play a part. But, while there is a multiplicity of factors which come into play, this does not exclude the probability that these various factors differ greatly among themselves in importance and that a few factors play a predominant rôle in edema. We shall therefore discuss separately some of the factors of the second and third class from this point of view.

The rôle of sodium chloride in edema

In the normal organism sodium chloride plays an important rôle in causing the retention of water in the body as a whole and in the fixation of water in certain tissues or organs. With a deficit of sodium chloride in the organism water is eliminated in an otherwise normal person. When a tissue is made poor in salt, water leaves the tissue. When there is lack of sodium chloride in the body, a lack of water cannot be made up very readily. On the other hand, a surplus of salt given with the diet leads to the retention of water. In the normal person the retention of water in the body is apparently, to a great extent, an osmotic phenomenon. We have reason to assume that sodium chloride plays a similar rôle in edema; only in edema a certain primary mechanism is disturbed and as a result of this alteration irregular distributions of sodium chloride take place apparently on a much larger scale than in the normal person, and the movement of water follows that of the sodium chloride. We know that a surplus of sodium chloride has a special tendency to be deposited in the skin and correspondingly here edema develops preferably. In general under normal, as well as under pathological, conditions a surplus of sodium chloride tends to be retained in the blood only for a short time, and if possible it is moved either to the kidney or deposited in the tissues; this latter process leads to edema; in certain cases, however this mechanism is interfered with and the salt may be retained for a longer period of time in the blood. Slight differences in the concentration of sodium chloride or water on both sides of permeable membranes lead to movements which tend to reëstablish the normal equilibrium. This equilibrium is a very labile one especially in normal persons as well as in persons who are ready to discharge their edema; a slight surplus of water or salt may lead to excess reactions.

With these views agree the many data concerning the movement and distribution of sodium chloride in renal insufficiency; we know likewise that in cardiac decompensation and in states of undernourishment there tends to be a retention of this salt. In pneumonia sodium chloride seems to accumulate in the lungs, and it is possible that also in other inflammatory foci a local retention of this salt occurs and that this fact contributes to the production of inflammatory edema.

While many researches concurrently indicate the great significance of sodium chloride in edema, it is necessary to point out that the majority of investigators made determinations merely of chlorine and not of sodium; the recent work of R. F. Loeb, Atcheley and Palmer has however shown that the distribution of these two constituents does not necessarily follow a parallel course. These investigators found an equal concentration of sodium in blood and edematous fluid; but in their cases endpoints in the equilibrium had probably been reached and these may have been preceded by an unequal distribution of sodium chloride between the blood and the tissue.

The rôle of proteins in edema

In certain respects similar to the rôle of sodium chloride is the part which proteins play in edema and in the distribution of water in general. Neither changes in the distribution of the sodium chloride, nor of the proteins play a primary part in the origin of edema; but both are concerned in the movement and distribution of water. We have found many instances in which proteins or other colloids influence the distribution of water. There are, however, also important differences between the sodium chloride on the one hand and the proteins on the other. It has not been possible to find any definite indications that changes in the concentration or character of the proteins determine the development of edema in a way comparable to the effect exerted by sodium chloride, and the amount of edematous fluid does not correspond to the protein content of the blood. We have found a marked independence in the development and discharge of edematous fluids of their content in proteins. We have seen that the effect of various substances on the water binding power of colloids, which Ellinger observed, does not correspond to the effect of these substances on edema.

While it does not therefore appear probable that the edematous retention of water in the tissue spaces depends mainly on the amount of protein which can pass through the capillary walls, owing to the increased permeability of the latter, still this protein must necessarily cause some retention of water and thus the protein must play at least a subsidiary rôle in the development of edema. It is therefore likely that the views of Eppinger, which are also sustained by the

experiments of Ellinger, hold good only in a restricted sense. At present we must however admit the possibility that future investigations may necessitate a modification of this conclusion, and it is especially the experiment of Morawitz and Deneke on the swelling of gelatin in uranium nitrate animals which, if substantiated, might perhaps point to a higher valuation of the significance of the interstitial proteins in edema. On the other hand, the views of M. H. Fischer as to the significance of organ colloids in the origin of edema, are not in harmony with the observed facts. This is true also of views of Hülse which, as far as we are aware, do not find any support in the known facts of the chemistry of proteins.

In particular as far as the views of Fischer concerning the effect of acid substances in edema are concerned, we have seen that, inasmuch as a part of the proteins exist in the body fluids as sodium proteinates, an increase in hydrogen ion concentration would tend to diminish rather than add to the water binding power of the proteins; on the other hand, the effect of an increased alkalinity might conceivably make more pronounced in a direct manner their water binding power.

Osmotic and diffusion potentials in edema

Osmotic and diffusion potentials help to regulate the exchange of water and salts between tissues or serous cavities and the blood and lymph. The experiments of Hamburger on the exchange between peritoneal cavity and blood, as well as those of Magnus on the distribution of hypertonic solutions of sodium chloride after intravenous injection, have proven the influence of osmotic and diffusion potentials in equalizing differences in concentration which originate in the body. We have learned in addition that various abnormal conditions may lead to localized alterations in the osmotic pressure within the organism. Thus we could show that following operations in general (Fleisher and Loeb) as well as after nephrectomy (Meltzer and Salant) the movement of water from the peritoneal cavity to the blood is accelerated in accordance with changes in osmotic pressure, which have been produced. We furthermore noticed that caffeine and adrenalin exert their effect on the movement of water and salt in accordance with osmotic changes which they call forth. In agreement with the observations of various investigators, we may conclude in

general that whenever edema tends to develop a retention of sodium chloride in the tissues is apt to have preceded this condition and thus presumably osmotic and diffusion potentials have tended to arise. As Priestly has made probable in the case of the diuretic effects of sodium chloride, very small differences in concentration of this salt may call forth movements of fluid leading to the elimination of water. Whenever sodium chloride is not sufficiently excreted, it tends, as we have seen, to accumulate in the tissue spaces rather than in the blood. It is significant that it is the distribution of the sodium ion more than that of any other substance which has a positive effect on the development of edema. This may be due to the fact that sodium can accumulate in the tissue spaces in a much greater quantity than any other ion and that at the same time it cannot readily penetrate into the cells or tissues proper; thus it accumulates in places where later edema develops, and presumably it is at least in part responsible for the movement of water into the tissues and for its retention in the tissue spaces. While thus differences in concentration are equalized, at the same time membrane equilibria, comparable to the Donnan equilibrium, become effective and lead to an unequal distribution of the sodium and chlorine ions.

It is of interest that some of the substances, which thus directly or indirectly create osmotic or diffusion potentials, tend also to alter the permeability of membranes; for instance, a changed equilibrium between sodium, potassium and calcium ions in the blood produces this result and in uranium poisoning the effect of substances like adrenalin and caffeine on the movement of water is lost perhaps on account of the alteration produced in the permeability of the membranes by uranium nitrate. It might be suggested that changes in membrane permeability may in some way affect the movements of salt and contribute to the creation of differences in concentration which lead to edema. The reversal of the current of fluid towards the tissue, which can be produced experimentally through the administration of caffeine in nephrectomized animals, or through the administration of pituitrin in diabetes insipidus, is also presumably the result of changes in concentration within the tissues; in this case also changes in permeability may possibly coöperate. Likewise the fact that in edema there is not only an increased current of fluid

towards the tissues, but also an inhibition of the reverse movement of fluid or salt from the tissues to the blood, suggests the activity of differences in concentration in causing a retention of fluid within the tissue spaces. We believe that the evidence which we have at the present time favors the conclusion that differences in the concentration of various substances in blood and tissue are at least partly responsible for the development of edema.

Localized edema

In many respects localized edema, and in particular inflammatory edema, is more favorable for the analysis of factors which cause edema than generalized edema. It is especially in localized edema that the great significance of changes in the permeability of the capillaries in edema was clearly established. Cohnheim and Lichtheim, as well as Starling, drew attention to local differences in the permeability of capillaries; furthermore there are local differences in the tissue pressure and local differences in the eliminating action of certain glands, like the salivary glands, which have likewise to be considered.

Inflammatory edema might almost be considered as due to the boring of holes through a dam, in consequence of which a local overflow of fluid occurs. In reality, however, such an increase in permeability is of a more complex character; it is graded and selective. Yet even in inflammatory edema other factors besides an increase in the permeability of capillaries probably come into play. Recent investigations have contributed much to the understanding of the factors which influence the permeability of capillaries and we are beginning to appreciate the complexity of these factors. A certain balance of ions influences the permeability of capillaries; potassium in particular seems to increase and calcium to decrease it; but under certain conditions an increase in the quantity of calcium may apparently lead to the opposite effect. The influence of potassium on the permeability of capillaries has a special interest in view of the fact that it has recently been found that the potassium content of the blood plasma is relatively increased in cases of edema. In addition carbon dioxide tension and hydrogen ion concentration, oxygen tension and certain hormones, like pituitrin and adrenalin, affect the permeability. All or the majority of these factors probably coöperate in regulating the

state of the capillaries. In general, it seems that a contraction of the capillaries is associated with a decrease, and a dilatation with an increase in permeability. In this connection it is of interest that we found indications of a similar condition in the case of the membrane of individual cells like the amebocytes. Chemical stimulation leads on the whole to a dilatation and to an increased permeability of the capillaries; this mechanism would therefore be favorable to an elimination of a strange substance. While thus much progress has been made in the analysis of the capillary permeability, some of the problems relating to inflammatory edema are not yet clearly understood. In particular the evidence as to the mechanism determining inflammatory dilatation of the capillaries and increased transudation is as yet somewhat contradictory.

While it is of great importance to study the localized behavior of capillaries, we must not forget that in the organism as a whole other factors besides the state of the capillaries have to be considered in the development of edema, and that the same substance may affect different mechanisms in a different manner; only in this way can we understand certain apparent contradictions in the evidence which we find in the literature. Thus we have seen that calcium affects the elimination of fluid through the interstitial wall, through the kidney and through the peritoneal lining each in a specific manner. In addition it has a specific effect on the heart action. Thus while calcium may under certain conditions prevent inflammatory edema, it may on the contrary increase the amount of peritoneal transudate; while usually it decreases urinary secretion, it may in certain cases accelerate the discharge of edematous fluid through the kidney.

Edema and the permeability of membranes

There are reasons for assuming that changes in the permeability of the capillaries play a considerable rôle not only in localized edema but in all kinds of edema. Yet if we consider critically the facts learned so far, our knowledge in this respect appears rather scant. We can be certain that changes in permeability play a great part in localized and in particular in inflammatory edema. In other cases there is also experimental evidence which renders it at least probable that factors which increase the permeability of vessels cause or contribute

to the development of edema. Reference may be made to the action of iodine, arsenic and chloroform, heat, of hematoporphyrine in combination with sunlight, of aromatic, fat soluble amins and other similar effects. We have seen that certain substances like thyroid, adrenalin, and calcium which have specific effects on the movement of water and dissolved salts, likewise affect the membranes of cells or tissues in a specific manner. Whether caffeine has a similar effect, seems uncertain at the present time. In general we have learned of the great variability in the permeability of cell membranes and the relation of these variations to functional changes in the cells. It is of interest in this connection that on the whole cells seem to be little permeable to fluids analogous to edematous fluid and this may be one of the factors which is responsible for the location of edema in the interstitial spaces rather than in the tissues proper.

It is natural that under those conditions we should be inclined to generalize as to the significance of an increase in the permeability of vessels. Yet we must confess that the evidence we have in the majority of cases of clinical edema, as to the significance of changes in the permeability of vessels, is either circumstantial or even contradictory. Thus in uranium nephritis earlier findings, indicating a more rapid elimination of sodium chloride solution through the capillaries, were not confirmed by later investigators, who, on the contrary, found a retardation; still it is possible that osmotic factors are implicated in the latter result. But we also found the movement of water and sodium chloride from the peritoneal cavity to the blood-vessels retarded and the specific effects of caffeine and adrenalin no longer clearly in evidence in uranium nitrate poisoning. On the other hand, Krogh and Harrop found a local increase in the permeability of the capillaries under the influence of uranium nitrate; and we may also refer to the observations of Morawitz and of Donner which indicate an increase in the vascular permeability in certain kinds of nephritis. In cardiac decompensation, the evidence again is circumstantial; we assume that the dilatation of the capillaries combined with an increase in carbon dioxide tension in the capillary blood may increase the permeability. Similarly circumstantial is the evidence in the case of hunger edema. In this state of our knowledge, it is difficult to give a positive answer to the question, whether edema

is primarily due to changes in the kidney, or in the tissues, or whether both factors are equally involved. The question may also be put in this way: Is the increase in the permeability of the vessels which communicate with the tissues dependent on an insufficiency of the kidney and subsequent retention of substances, or is it a primary factor independent of the kidney function. We have seen that we cannot answer this question with certainty; but we consider it probable that both a retention of substances and a change in the capillary permeability play a part.

As to the variables which determine the movement of fluid through membranes and especially through capillaries in the living organism, we have to consider (1) osmotic and diffusion potentials and the specific effects of proteins; (2) electrostatic forces, electro-endosmosis, abnormal osmosis; but of the action of these in the development of edema, we are ignorant at present; (3) capillary forces, (4) factors depending upon the state of contraction of the living units which compose the membranes. As already stated in general a state of contraction decreases the permeability and dilatation tends to have the opposite effect.

Hydremia and edema

We have seen that injections of large amounts of an isotonic sodium chloride solution leads to the formation of transudates in the serous cavities and to the collection of fluid in the interstitial tissue spaces in certain areas, but not generally in the subcutaneous tissue. In this case we have to deal both with a hydremic change in the composition of the circulating blood, as well as with an increase in the quantity of the fluid, with therefore a polyemia. These factors then in themselves are not sufficient to cause typical subcutaneous edema.

Under a variety of conditions there may be in the blood, according to a number of investigators, a hydremia and polyemia or on the contrary an inspissation of the blood. These conditions are usually diagnosed by following the variations in the refractive index of the blood plasma, which indicates the amount of protein in the plasma, or by following the variations in the number of erythrocytes. Neither of these methods can give absolute values for quantity of blood or plasma; but so far as the quantity of protein is concerned, it seems to

be a much more variable factor than the erythrocyte count, especially since it has become known that proteid may enter and leave the blood-vessels under various pathological or experimental conditions. We may attach a comparative value to successive determinations of the variations in the number of erythrocytes. From all the investigation it follows that there is no direct relation between the state of dilution or inspissation of the blood and the development of edema. However, in hydremia there may be a subsidiary factor which, especially in association with other factors, may favor the production of edema.

Blood pressure and edema

Blood pressure as such is a factor in the development of edema; we have seen that a lowering of the blood pressure below a certain point prevents the occurrence of inflammatory edema. There are some indications that an increased filtration pressure, due to a rise in blood pressure, may under certain conditions cause edema or at least be a contributory factor to it. Thus in edema of the lung a marked rise in blood pressure may in some cases be responsible for the pressing out of fluid into the interstitial tissue and into the alveoli of the lung. In the portal system also an obstruction to the outflow of venous blood and increased capillary pressure may lead to increased transudation and lymph formation (Starling, Manwaring), and it is possible that the effect of adrenalin on the peritoneal transudate may be due to an increase in filtration pressure in the portal area. But in the majority of cases we find no direct connection between a rise in blood pressure and the development of edema; this is especially noticeable in cases in which the rise in blood pressure is due to renal disease. Furthermore usually under conditions in which a rise in blood pressure is found, other changes are associated with the alteration in blood pressure and these associated changes may lead to an increased permeability of the vessels and thus to edema. Taking all these facts into consideration we may conclude that an increased filtration pressure can represent at best only a factor of minor importance in the origin of edema.

We find thus indications that a multiplicity of factors is responsible in a similar manner for the distribution and movement of fluid in the normal organism and under pathological conditions, but that the importance of the various factors in the origin of edema differs greatly.

Changes in the permeability of capillaries acting jointly with differences in the concentration especially of sodium chloride seem to be mainly responsible for the abnormal retention of fluid in the interstices of the tissue and in the serous cavities. An abnormal distribution of proteins may play a contributory rôle. Other factors which we named are of less importance; they may act either indirectly by influencing the first named factors, or directly under special conditions.

The last fifteen years have contributed much to the understanding of different types of edema; and the analysis of the movement of water and dissolved substances from one part of the organism to another, of the factors which regulate the permeability of the capillaries, and of the conditions which determine the power of colloids to attract water, has much increased our knowledge. New views have been opened through the discovery of substances which affect the movements of fluid in the organism in a specific manner. Yet, after all, our understanding of the interaction of those factors which determine the normal distribution and movement of water in the organism is still incomplete; and this is true also of the interaction of these factors in edema. Even our knowledge of the changes in the permeability of capillaries in edema is fragmentary and at present we cannot exclude the possibility that instead of the increase in permeability which has been definitely proven in certain cases there may not be in other cases on the contrary a decrease in permeability which would make it possible for changes in concentration of various substances to develop. There are certain fields, as for instance, the significance of electrostatic forces in the movement of water under pathological conditions, about which we are in ignorance at the present time; our understanding of the relations between proteins and water is likewise still incomplete in several respects. We can therefore regard all general conclusions as to the development of edema at the present time merely as tentative, and we must expect that additions to our knowledge in the near future will necessitate a revision of some of our present conceptions.

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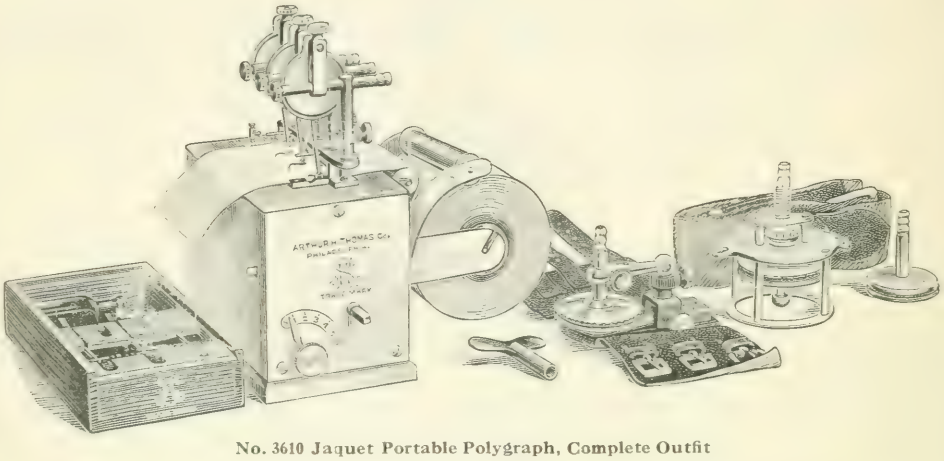

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THE ETIOLOGY AND PATHOGENESIS OF RICKETS

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The development of knowledge regarding that widely prevalent disorder of children known as rickets has not been in logical sequence. In this respect rickets is similar to other well known diseases. A symptom complex is described and before its causation is clear or even the pathological processes underlying it understood, a perfectly satisfactory remedy is discovered. As has been the case, in other instances so here no one knows to whom the credit for the remedy is due.

The student of rickets can point to several different landmarks or milestones in the line of progress. First unquestionably is the monograph of Glisson which appeared in 1650, the first monograph on disease ever published in England. It contains evidence of most careful observation and is further noteworthy in that there is included the mention of scurvy as an infantile disease. Glisson developed his ideas during a number of years but almost certainly he was not the first to recognize rickets. Its presence was well appreciated by the populace in certain parts of England probably better than by physicians and the name "Rickets" is found in the Bills of Mortality seventeen years before the appearance of Glisson's monograph. But the monograph was and is a masterpiece that greatly influenced the medical thought of Glisson's day and of a good many days after him.

The second is the monograph by Pommer in 1885 which established the pathology of rickets upon a firm foundation. Before that time many of the abnormalities of the newly born child such as chondrodystrophy and osteogenesis imperfecta had been considered rachitic in origin, even by Virchow himself. It followed that the belief was implanted in the minds of many that rickets may be and frequently is a congenital disease. It took many years to eradicate this belief.

It is perhaps more correct to say that the belief died with those who held it rather than that they themselves ever gave it up. Pommer showed convincingly that there are definite and characteristic changes in the bones of patients with rickets which are not present in the bones of the newly born.

Between these two milestones that have been mentioned there should be a mark roughly half way between the two but exactly where situated and by whom placed it is impossible to say. It should stand somewhere to serve as a monument to the intelligent empiricism that has given such remedies as digitalis, quinine and mercury to medical practice. The origin of the use of cod liver oil is obscure. Trousseau wrote that he learned its value from Bretonneau and he in turn from the father of a patient whose older brother had been successfully treated by cod liver oil in Holland. Trousseau speaks of the common practice on the shores of the Baltic Sea of giving cod liver oil and ray liver oil to weakly children and valetudinarian adults.

Finally the milestone erected in the last five years by a number of different workers who have regularly and consistently produced rickets by different means in a great number of animal species and thus have made possible an intensive study of all its different aspects.

But of course there have been other observations and studies of merit. There is the appreciation by Petit in 1723 that rachitic bones are soft. Glisson, who perhaps had paid chief attention to the deformities in the stage of repair, had believed that they were unduly hard. There are the careful chemical studies on the composition of the bones by Marchand, Friedleben (made with the same accuracy and meticulous attention to detail which he devoted to his beloved thymus gland), by Brubacher, Gassmann and others. There are the metabolism experiments chiefly of Schabad and E. Schloss. There are the determined attempts by E. Voit, Aron, Stoeltzner, Dibbelt, Heubner, Schmorl and many others to produce rickets in animals, none the less praiseworthy because they were usually unsuccessful. There are the observations by Huntly, Palm, Raczynski, Huldschinsky, Hess and Unger and others upon the preventive and curative effect of sunlight and the ultra violet rays from different sources. All in all the list of those who have made contributions of importance to the study of rickets is a long one.

One might readily ask and the question is distinctly germane to the subject of etiology, why was it reserved for Glisson to write this monograph? Why did a disease which often gives such striking objective evidence of its presence pass nearly unnoticed? With our present knowledge the question is best answered by saying: because it is a disease of recent origin. If it existed in ancient times it did so infrequently and sporadically as the result of some unusual combination of circumstances. There are good reasons for such an answer. With the exception of a few rather vague references to infantile deformities, one for instance by Soranus, there is no description of anything like rickets in old medical literature. And this is the more striking because the ancients were excellent observers. The foundation of the Hippocratic and Galenical systems was objective symptomatology. Had the symptoms of rickets been available for observation doubtless they would have been recorded.

There were others besides physicians with an eye for the physically abnormal and grotesque. There were the artists, the sculptors of the statues and bas reliefs of Egypt, Greece and Rome. The Queen of Punt, evidently a chondrodystrophiac, was affectionately portrayed in all her royal and grotesque proportions; the Egyptians had the gods Ptah-Sokar and Bes, both chondrodystrophiacs, of whom they made statuettes and they portrayed also pygmies and ateleiotic dwarfs. The bow legs and knock knees, the curvatures of the femora and tibiae, the thoracic and cranial deformities would have delighted the ancient sculptors. Nothing has been found that bears any resemblance to rachitic deformities.

There are also very ancient bones available in large numbers chiefly from Nubia and Egypt, a few from the Baltic coasts and many from Peru. There is no evidence to be deduced from them that rickets prevailed among those peoples but according to Lortet of Lyons there are rachitic changes in the bones of monkeys that were confined in the temple of Thebes two thousand or more years ago. It is as if the ancients had preserved their experimental efforts for the benefit of posterity. There are bones also of more recent date in the old crypts and charnel houses of England. All bear striking testimony to the freedom from rickets of man up to the beginning of the seventeenth century and the gradual increase of the disease after

that time, an increase which has been taking place up to the present. This brings us face to face with the magnitude of the problem. There are clinical and pathological statistics in sufficient number to attest that from the latitude of the middle of Italy to the north of Scotland from 75 to 90 per cent of the artificially fed children in the cities of Europe and America are the victims of rickets in the winter and spring months. Other parts of the world have rickets but in them it is not nearly so frequent or so severe. Rickets exists outside of cities and afflicts also the rich but it is the poor population which suffers most and usually in proportion to its poverty and unhygienic manner of living.

Rickets is a disease that contributes greatly to infant mortality by diminishing the resistance of the young child to all forms of infectious disease. It stunts and deforms the body and influences adversely the efficiency of the man power of a nation. The recognition of this fact in England has doubtless been partly responsible for the great activity in the study of rickets fostered by the Medical Research Council.

The attempts to produce rickets experimentally in animals, usually in dogs, began shortly after it became clear that in rickets there is regularly a diminution of calcium salts in the bones. It seemed logical to reduce the calcium of the diet. This was done by Weiske, Voit, Stoeltzner, Dibbelt, and a host of other experimenters. It cannot he said that they never produced rickets (it is likely that Dibbelt and Aron occasionally did) but the disease was never regularly produced. There were two chief reasons why the attempts must have been unsuccessful. There was no knowledge regarding the accessory food factors and the effect of sunlight was not appreciated. Therefore, it came gradually to be believed that a reduction of calcium in the diet would bring about osteoporosis but not rickets.

Despite these negative results there is a very large literature upon primary calcium deficiency as a cause of infantile rickets. The amount of calcium that children should retain during the first year has been calculated. It has been emphasized that the margin between the amount of calcium received in woman's milk or in diluted cow's milk, and the amount that should be retained is narrow. There is, therefore, the constant menace of rickets. Schabad has gone so

far as to say there is a pseudo-rickets due to calcium deprivation, similar to the physiological osteoporosis of Schwalbe, which cannot be differentiated from infantile rickets. The evidence in favor of calcium deficiency as a primary cause of rickets will be considered later.

The older attempts to produce rickets by diets deficient in phosphorus were few in number, and also unsuccessful. The younger Heubner produced a change somewhat similar to scurvy but it was not rickets. Schmorl could do no better.

Observations by Bland-Sutton at the London Zoo and the results of the treatment that he instituted there more than twenty-five years ago have had a great influence upon pediatric thought and practice. It is difficult to make out exactly what Bland-Sutton himself thought because he never published his observations. The litters of lion cubs had died regularly as the result of extreme rickets. Bland-Sutton advised varying the diet of horse flesh alone, which the cubs had usually received after weaning, with milk, pounded bones, and cod liver oil. One infers from Cheadle's account that the effect was completely satisfactory. Findlay's version is not so favorable. Whether the treatment was a complete or only partial success it became implanted in the minds of many that fat deprivation played an important part in the causation of rickets, a view which seemed to receive substantiation from the frequent development of rickets in children receiving condensed milk or proprietary infant foods. The view was also strengthened by the favorable influence of cod liver oil.

Chronologically the experiments of Findlay of Glasgow require consideration. This consistent student of rickets attempted to produce it in puppies by giving them a diet composed largely of carbohydrates with a minimum of fat. He was not able to do so when the animals were allowed their freedom but could when they were closely confined. He came to the conclusion that it was the lack of fresh air and exercise that produced rickets in his animals, *ergo* it was the same environmental influences that produced rickets in animals in the zoo or in infants in their homes. It is seen that Findlay postulated the etiological factors very definitely. The responsibility rested upon the *lack of exercise* and *fresh air.*

Findlay was unaware of the paper by von Hansemann published at nearly the same time in which the latter expressed his widely quoted ideas upon domestication. Von Hansemann like Bland-Sutton had been greatly interested in the subject of rickets in animals in captivity. He pointed out that wild animals were never afflicted with rickets, which is a scourge to those in confinement, and that all animals that had been domesticated by man, such as horses, cows, sheep, pigs, dogs, all but the cat spontaneously develop rickets in captivity. Von Hansemann went further and stated that in the child rickets is the result of domestication. When man domesticated animals he had domesticated himself. He had shut himself up in houses, he had covered his children with tight clothes and had excluded the air from them and he had gradually come to eat a refined diet and one that was unphysiological. Von Hansemann thought that diet might play some part in the production of rickets but it was the wearing of clothes and the lack of air that were chiefly to blame. Von Hansemann and Findlay have been the apostles of "environment" and Findlay has been an active and ingenious experimenter in favor of his views. He has attacked vigorously the divergent views of others.

We have seen that until recently it has seemed impossible regularly to produce rickets in animals. To Edward Mellanby belongs the credit for showing that this can be done, as well as for bringing forward many facts of importance. He fed puppies on diets consisting of a minimum of skimmed milk, with an unlimited amount of bread, and with salt, orange juice, and yeast. His experimental diet has undergone modifications. For our purpose it is not necessary to consider them. To the basal rickets-producing diet he added different oils and fats, meat and other things in order to test their value as antirachitic agents, preventive and curative. Briefly summarized his results showed that animals on the experimental diet regularly develop rickets, that cod liver oil is superior to all other fats, that butter fat has also an antirachitic influence whereas the vegetable oils are almost without effect. Further he demonstrated that cod liver oil heated for four hours at a temperature of 120°C. retains its power to overcome rickets but that of butter is nearly lost. Mellanby drew his conclusions with some reserve in saying

that the substances which prevent rickets, especially cod liver oil, are rich in fat soluble A and that fat soluble A is probably the antirachitic vitamine. But no reserve was shown in the report of the Medical Research Council which stated categorically that rickets is due to a deficiency of fat soluble A. The issue was thus well joined between those who find the cause of rickets in environmental conditions and those who find it in diet. There seemed no possibility of compromise, no uniting on common ground.

Findlay and Noël Paton repeated Mellanby's experiments with animals that were kept in the country. These remained free from rickets. Those confined in the laboratory became rachitic. Small wonder then that the workers in Glasgow stuck to their guns and to their belief that environmental factors are the all important factors. Mellanby confined animals on a good diet and no rickets resulted. No greater wonder that to him rickets was dietetic in origin.

Mellanby demonstrated the remarkable curative effect of cod liver oil on rachitic animals. By means of successive radiograms Park and I had already observed the same effect with rachitic children. But Trousseau by clinical observation alone had long before estimated cod liver oil at its true value. He knew that it would cure rickets. He made also the sharp observation when mentioning substitutes for it, that butter is one but that of this a very large quantity is necessary, as much as 60 grams a day.

In cod liver oil rickets has more than met its match. On any diet that will support the life of a human being or an animal cod liver oil will, in all probability, prevent or cure rickets. Its effect is astounding. With the utmost regularity it causes the deposition of lime salts in the bones. The effect is not manifest at once as two or three weeks must elapse before radiographic evidences of healing can be seen. For this reason there has not been complete unanimity regarding the therapeutic effect of cod liver oil. In the last thirty years it has been employed in rickets, perhaps by most physicians, with not much more enthusiasm than they have prescribed it for tuberculosis or malnutrition. It was considered an easily assimilable form of fat. Observations of the last few years metabolic, chemical and radiographic leave no further doubt whatever that it is a specific remedy of the first rank. Too much cannot be said in its favor.

The conclusion is inevitable that later generations threw away what the previous had gained and that the critical judgment of some of the older clinicians was better than that of their successors. It is worth while to emphasize the effectiveness of cod liver oil against rickets because this fact must influence our views regarding the character of the disease.

The remarkable series of experiments which have been carried out in this country by Sherman and Pappenheimer and McCollum, Park and their co-workers have greatly illuminated the whole subject. Rats which are very favorable subjects for many reasons have been employed as test animals. The diets have been of great variety but whenever desired absolutely constant in composition. The experiments have been controlled by histological studies and sometimes by chemical examinations.

The experiments by these two groups of workers were carried on almost synchronously. Recently their results, so far at least as calcium deprivation plays a part, have been completely confirmed by Korenchevsky. For the sake of simplicity the results may be summarized together: Though the variations may be innumerable, there are two chief types of diet upon which young animals, after an interval of some weeks, become rachitic, one in which the calcium is very low and the other in which the phosphorus is diminished. The action of these diets is more pronounced if, in the low calcium diet, phosphorus is present in plentiful amount and if, in the low phosphorus diet, the calcium is in excess. With any diet rickets may be prevented or cured if it is composed of cod liver oil to the extent of two per cent or more. The same is true of other fish liver oils. Shark liver oil and burbot liver oil seem equally efficacious. A large amount of butter fat, 15 per cent or more, is required to accomplish the same purpose. (Compare this with the excellent observations of old Trousseau.) Suet has some favorable effect, lard and the vegetable oils almost none. A good salt mixture even in the absence of more fat soluble A than is just required to prevent the development of xerophthalmia acts as a barrier to the entrance of rickets. The experiments can be repeated and results obtained with nearly mathematical accuracy. If butter and cod liver oil and a good salt mixture and eggs, as Mellanby has shown, will prevent and cure rickets,

(doubtless a number of other articles of food will do the same), it is impossible to escape the belief that rickets is a dietary disease. It can be produced at will by diet, it can be cured at will by diet. An experiment of McCollum and his collaborators indicates very strongly that there is an antirachitic factor distinct from fat soluble A. Cod liver oil may be heated sufficiently high and sufficiently long to destroy its power to cure xerophthalmia, the test for the presence of fat soluble A, but after such treatment there appears little if any diminution of its power to cure rickets.

But with dietetic measures our ability to prevent or cure rickets is by no means exhausted. There appeared in 1889 in the Rajputana Mission Press (a publication in which one would hardly expect to find revolutionary views regarding disease) an article by a Dr. William Huntly entitled, "Habits and diets of the natives of Rajputana with reference to the etiology and treatment of rickets." Huntly described the wretched diet and living conditions of the natives judged by western standards and yet their freedom from rickets. In his paper occur these significant words "What have they then to counter-balance the evil of the filth and diet surrounding them? The answer I think is sunlight." In the following year, 1890, Theobald A. Palm, also a medical missionary, published an extensive article on sunlight as the cure for rickets, with the results of a questionnaire form of inquiry addressed to people, chiefly missionaries, in many parts of the world. He also had no doubt as to the influence of the sunlight. He urged an exact study of the subject and wrote "It is important that the sunshine recorder be of the form which indicates the chemical activity of the suns rays rather than its heat." A generation after him his suggestions have been followed.

The first indubitable evidence of the beneficial effect of the sun's rays was furnished by Raczynski in 1912. He subjected to chemical examination the bodies of two puppies of the same litter, nursed by their mother. One puppy had been kept in the sunlight the other confined in the dark. The body of the first animal contained much more calcium and phosphate than did that of the second. The evidence furnished was not voluminous but it convinced Raczynski that deprivation of sunlight was an important factor in the causation of rickets and he believed that his experiments corresponded with

clinical observation. Huldschinsky, in 1919, reported his results with the treatment of rickets by means of radiations from the mercury-vapor quartz lamp. The clinical and radiographic evidence was absolutely conclusive first, that he was dealing with rickets and second, that by this means a cure was accomplished. Since that time a large number of observers have corroborated his statements as to treatment with children and have shown also the preventive and curative effects of the radiations from this source with experimental animals. Huldschinsky used sunlight in addition, Riedel sunlight chiefly, but it was probably Hess and Unger who first used sunlight alone and were able to demonstrate that it was effective without the assistance of emanations from any artificial source. Just as radiations from the mercury-vapor lamp prevent and cure rickets in children and experimental animals so does sunlight accomplish the same results. Without attempting any quantitative comparison which we are not in a position to do, we can say that the radiations from these sources are thoroughly effective against rickets just as cod liver oil is thoroughly effective. Rickets is capable of control by two masters but apparently how widely different! One is dietetic, the other environmental. It therefore seems possible to look at the disease so far as its etiology is concerned in two ways. One may say that it is a dietary disease; but then it is necessary to admit that it may be prevented or cured by pure environmental influences (sunlight). Or one may say that it is due to defective environmental influences and if so one must admit that it can be cured by cod liver oil and other articles of diet. If Findlay had not emphasized lack of fresh air and exercise so particularly but had included all environmental factors including sunlight he would have been very near the truth and if the Medical Research Council had not so definitely committed themselves to fat soluble A but had included the substances closely identified with it in nature they would have been partly right.

With the facts that are now in our possession we are in a position to offer an explanation for many things that have troubled the writers of the past and when we do so we are impressed more and more with von Hansemann's ideas even though he perhaps underestimated the influence of diet and did not recognize the all powerful effect of the sun. For man *has* domesticated himself, he *has* shut his children

up in houses to their detriment and he has fed them upon a diet that allows rickets to develop.

Perhaps the first step toward rickets was taken when women began to lose the ability to nurse their children. Woman's milk is no absolute safeguard against the development of rickets. Certainly one sees enough rachitic children exclusively breast fed to make that point clear but the artificially fed who are rachitic outnumber the breast fed five or ten to one. No one has yet succeeded in finding out wherein the protection lies.

When artificial feeding becomes necessary ample opportunity is given for rickets to develop. It is the custom to confine infants for many months, whether wisely or unwisely it is not necessary to discuss at present, to a diet composed almost exclusively of cow's milk more or less diluted and with carbohydrates added. Upon such a diet, children become rachitic unless protected in some particular way, even if there is an abundance of fresh air and they are allowed to take exercise in whatever way their age permits. This has been common knowledge from hospital experience. The carefully controlled observations of Chick and her collaborators drive home the truth with added force. Ninety per cent of the children in the Vienna Kinderklinik who were used for observations, with the best food and care obtainable showed unmistakable radiographic signs of rickets in the course of the winter and spring months, when housed. Rickets was absolutely prevented by a small amount of cod liver oil given to the children used for control observations. When the rachitic children were out of doors in the sun the rickets was rapidly cured. Those who were out of doors at night and not in the day time remained unimproved.

In this connection may be mentioned the study of the social and economic factors in the causation of rickets carried out in Glasgow, a hot bed of rickets, by Miss Ferguson under the direction of Noël Paton and Findlay. A large number of facts was collected regarding the families of rachitic and non-rachitic children and their manner of living. Among others the conclusion was reached that food played no part in determining either the onset or the severity of the rickets; that inadequate air and exercise were potent factors. To one looking at the figures, perhaps from a prejudiced standpoint, it

seems that the most important information adduced was that the number of children in a family and the health of the mother had a profound influence, that the Garden Cities of Bourneville and Port Sunlight (the very name is suggestive) where control studies were made were practically free from rickets and most of all, that of the severely rachitic children 45 per cent were not taken out of doors at all while only 4 per cent of the non-rachitic were continuously housed.

No perfect diet for infants other than woman's milk is known and even that is frequently not perfect. The deficiency of the artificial diet is very often compensated for by exposure to the sun or by some food such as cod liver oil. The children of the poor who live in streets dark enough at best, who are given inadequate food and are taken out of doors infrequently are sure to be victims of rickets in the winter and spring months. Major Hutchison's remarkable observations in India duplicate the original ones of Huntly in showing the extraordinary power of sunlight to protect the natives from rickets though they employ a wretched diet. But Hutchison had the added advantage of having for controls women and children of a higher caste living in the same town who observe a remarkable custom. The children are kept in doors, part of the time nearly in the dark, until they are two years old. The girls from the time of their marriage which takes place when they are about twelve years of age, never go out of doors unless heavily veiled and then infrequently. These people though eating a much better diet than the very poor suffer severely from infantile rickets and from the so-called rachitis tarda of older childhood and adolescence. The reason for this seems quite plain.

The explanation that rickets is a disease usually of the first two years is doubtless that after that time the diet is varied and the child capable of reaching the sunlight out of doors by his own efforts. Sunlight protects children in the tropics and temperate zones at all times of year and doubtless those even in the far north in summer. The freedom from rickets of children in the northern parts of the world in the winter time must be referred to their diet. Natives eat fat in abundance, they eat all the parenchymatous organs of the seal and fish when they can obtain them. Fish livers are dain-

ties. The children of the north by eating what they can get to eat are protected and it would be difficult for a native of the tropics to keep out of the sun.

The first homes of civilization were in tropical or semi-tropical countries. It is therefore no surprise that so far as we can discover rickets was nearly or quite unknown in Egypt, Nubia and Peru. Farther north, in England for instance, an explanation must be found for the freedom of the population for many centuries followed by surrender to the foe. This appears to be found in the sociological or economic conditions. According to Rogers the population of England in the fifteenth century was about two and a half million, the same as it has been for three centuries. The population was rural, the cities small. The London of 1500 had 35,000 inhabitants and the next largest town was York with 11,000. The housing of the people as a whole was wretched. The poorer classes lived nearly as much out of doors as within doors. The conditions were practically the same in Glisson's time. The fact that he found rickets more common in the families of the well to do is suggestive. Then came the period of industrial growth, the people crowded together. The total population more than doubled in a century and that of the cities many times. Wealth accumulated and men decayed or their teeth did. The process has been continuous to the present time.

The knowledge gained in the last five years has seemed to establish the etiology of rickets upon a firm foundation. There is no reason to suppose that this will be shaken. There has been a fortunate combination of statistical observation and experimental proof.

While we are thus in possession of the facts regarding the conditions under which rickets occurs and how it may be successfully treated they do not explain why it arises, why the bones are deficient in lime salts and what are the processes by which rickets is cured. Korenchevsky has well expressed the thought that has been in the minds of many. "There is no doubt that the key to the problem of rickets is to be found in the discovery of the cause which prevents the deposition of calcium salts into the bone and bone forming pro-

liferous cartilage." Gideon Wells devoted a large part of his excellent Harvey Lecture twelve years ago to certain questions:

Why is calcium deposited in the tissues at all?

Why is it deposited in some tissues and not in others?

Why is the composition of calcified deposits so constant, qualitatively and quantitatively?

What are the causes of rickets and osteomalacia?

Lehnerdt wrote an interesting monograph entitled "Warum bleibt das rachitische Knochengewebe unverkalkt?" All of these authors were seeking an explanation for the failure of the same phenomenon; viz., the selective deposition of calcium salts.

Eight years ago Marriott and I began to work on this problem. We appreciated that it was impossible to proceed far unless we were able to determine the concentration of the elements which compose the major part of the inorganic salts of bone, calcium and phosphorus, in the fluid from which the bones receive them, i.e., the serum. There were no methods applicable for the detection of these substances in the small amounts of blood that can safely be obtained from infants. Marriott, Haessler and I devised methods which more recently have been superseded by a number of better ones. It can be said, however, that the methods that we first used gave results similar in every way to the new methods.

Marriott and I first studied tetany in a long series of observations and were able to show that, with the symptoms of the so called idiopathic form of infancy, a marked reduction of the calcium of the serum can be determined. From a normal level of 10 to 11 mgm. per 100 cc. of serum the calcium may sink to a level of 7 or even 5 mgm. The results are emphasized not for the purpose of discussing tetany, for it is particularly desired to avoid that subject at the present time, but because rickets is invariably associated with tetany. Rickets may exist quite without tetany, but idiopathic infantile tetany does not exist without rickets. In 1916 Marriott and I determined the calcium concentration of the serum of a few cases of rickets without evidences of tetany and found it normal or slightly reduced. Tetany may gradually impose itself upon simple rickets. One must be sure on this account to choose absolutely uncomplicated cases of rickets for study.

In 1919 Kramer and I began a systematic study of rickets. We confirmed our previous findings, i.e., that in rickets the calcium of the serum may be reduced to a small extent but (and this is the matter of chief importance) severe rickets with marked deformities and extensive radiographic changes may exist with no demonstrable change in the calcium concentration. We further found, and the observation was coincidently made by Iverson and Lenstrup in Denmark, that the concentration of inorganic phosphorus in the serum in cases of uncomplicated rickets is regularly much lower than it is with normal, young children. The breast fed infant has an average of about 6 mgm. per 100 cc. of serum, the average for the healthy artificially fed is a little lower, about 5.5 mgm. while the rachitic infant has 3.5 mgm. or less. In one instance it was as low as 0.8 mgm. To this rule, of the reduction of inorganic phosphorus, no exception has been seen. In the last 72 cases observed the average for the inorganic phosphorus has been 2.5 mgm. a reduction of more than 50 per cent. In the same cases the average for the calcium has been 9.6 mgm., a reduction of approximately 5 per cent. Whether the diet is woman's milk or cow's milk the result is the same. These figures do not lend much support to the view that perverted calcium metabolism is the all important factor in rickets or that rickets is due to a calcium deficiency either because it is not furnished in sufficient amount in woman's milk or because it is not sufficiently absorbed from cow's milk. The findings with regard to the phosphorus are the more remarkable because a child receiving undiluted cow's milk may ingest nearly seven times as much phosphorus as does the breast fed child and yet the phosphorus of the serum of the former may be only half that of the latter.

How is it with the experimental animal such as the rat? We have had the good fortune to be able to make determinations on the blood of the animals studied by McCollum and Park. Dr. McCollum very kindly placed these at our disposal. It has previously been stated that there are two chief types of rickets-producing diets, the one very low in calcium with a moderate amount of phosphorus, the other relatively low in phosphorus with a very high calcium content. With each diet there is just enough butter fat to allow growth and prevent sore eyes. The normal rat has a calcium concentration

of 10 mgm. and an inorganic phosphorus concentration of 8 mgm. per 100 cc. of serum. The rats on the low calcium diet have a normal phosphorus concentration but only 4.5 mgm. of calcium in the serum instead of 10. The rats on a low phosphorus diet have a normal calcium concentration but the phosphorus is only 2.5 instead of 8 mgm. per 100 cc. of serum. Here then are two diets widely different only so far as the inorganic elements are concerned, that bring about quite different concentrations of calcium and phosphorus in the serum and yet on each diet rats develop rickets with similar macroscopic changes and microscopic changes that differ in degree rather than in kind.

When these animals, irrespective of the diet they have been receiving, are treated by the same means that are used therapeutically for children, i.e., by cod liver oil, by ultra violet radiation or by sunlight, a rapid healing of the rachitic lesion occurs and calcium phosphate is deposited in the bones. It should be emphasized that the deposit is calcium phosphate no matter what the diet has been and no matter which element, calcium or phosphorus, has been reduced in the serum. Further: as the result of these measures a change of concentration in the serum takes place so that with the child the phosphorus increases and with the rat the calcium or phosphorus (whichever was reduced) increases, and eventually there is a return to a normal concentration. The process is very rapid in the rat and considerably slower in the child. As might be expected, the changes in the serum may be detected before the radiographic evidences are appreciable. The cure is the more remarkable in the case of the rat because, while the child is usually receiving a considerable quantity of calcium and phosphorus in his food, the rat receives in the one instance a diet which contains only 0.05 per cent of calcium. Yet he brings his calcium concentration up to the normal. Moreover, reproduction is possible in these rats to the third and fourth generation, if cod liver oil is continued, but the concentration of calcium in the serum of succeeding generations gradually falls.

As the result of these findings upon the concentration of the calcium and phosphorus in the serum of children with rickets and tetany and of rats with rickets are we in a position to answer the questions of Wells, "Why is the composition of the bones and of calcified tissue

so constant?" and "What is the cause of rickets?" as well as the question of Lehnerdt "Warum bleibt das rachitische Knochengewebe unverkalkt?" Let us attempt it but let us appreciate at the outset that the explanation must be broad enough satisfactorily to account for normal calcification, the failure of it in the rickets and tetany of children where the calcium may be low or normal, and in the rickets of rats irrespective of the diet. Gideon Wells emphasized that there is no acceptable evidence that in calcification the deposition of calcium is initiated as a chemical precipitation due to some particular recipitating ion, a "Kalkfänger," which is present in the tissues to be calcified and not elsewhere. He believed that calcium deposition depends more on physico-chemical conditions than chemical reactions though it is essentially a precipitation of calcium salts, usually in a hyaline matrix such as cartilage or bone. Tricalcium phosphate which composes from 85 to 90 per cent of the mineral matter of bone is a very slightly soluble salt. Such salts obey certain well known laws and their behavior in solution may be prophesied with absolute certainty. Let us consider for instance the equilibrium existing in a saturated solution of silver chloride under definite and unvarying conditions in contact with solid silver chloride. It may be represented by a formula as follows:

$$\underline{\underline{AgCl}} \rightleftarrows AgCl \rightleftarrows Ag^{+} + Cl^{-}$$

that is, solid silver chloride is in equilibrium with molecular silver chloride in solution, and this in turn with silver and chlorine ions. The Mass Law governs the relationship between the ions of silver and chlorine and the molecular silver chloride. This is represented by a formula which holds invariably under definite conditions. It is as follows:

$$\frac{[Ag^{+}] \times [Cl^{-}]}{[AgCl]} = K$$

that is, the product of the ionic concentrations of silver and chlorine divided by the concentration of the molecular silver chloride is a constant. Since the concentration of the molecular silver chloride is a constant figure it may for simplicity's sake be disregarded and we may then write the formula simply $[Ag^{+}] \times [Cl^{-}] = K$. This K

is the so-called solubility product constant. It differs with each salt. It cannot be exceeded without precipitation taking place. For instance: If to a saturated solution of AgCl some soluble salt with a common ion such as NaCl be added the chlorine ions in the solution are increased and the solubility product constant is exceeded. Precipitation takes place until the constant is reëstablished. Similarly by adding a soluble silver salt, silver nitrate, the product constant is exceeded and precipitation occurs until the constant is reestablished. It is quite evident that the precipitate in each case is silver chloride. If on the other hand the solution is not saturated the product of the anions and cations is less than the solubility product constant. Silver nitrate or sodium chloride may then be added up to the saturation point without precipitation occurring and if solid silver chloride is introduced some of it will be dissolved, but slowly and with difficulty for comparatively insoluble substances precipitate much more readily than they dissolve.

Tricalcium phosphate, $Ca_3(PO_4)_2$, is such a substance soluble only to a slight degree. In the serum, tricalcium phosphate is subjected to the influence of carbonic acid which is present in considerable concentration. We may write the formula as follows:

$$Ca_3(PO_4)_2 + 2H_2CO_3 \rightleftarrows 2\,Ca\,H\,PO_4 + Ca\,(H\,CO_3)_2 \rightleftarrows 2\,Ca^{++} + 2\,H\,PO_4^{--} + Ca^{++} + 2\,H\,CO_3^{-}$$

If calcium phosphate is exposed to the action of carbonic acid an equilibrium is established between dicalcium phosphate and calcium bicarbonate and between these and calcium, HPO^{-}_{4} and HCO^{-}_{3} ions. When the CO_2 tension of this solution is reduced a reversal of the process takes place and tricalcium phosphate is precipitated again. The reduction of the CO_2 tension in a solution containing HCO_3 ions is equivalent to increasing the pH, i.e., the alkalinity. The determination of the free ions in heterogeneous mixtures has not been made, as it is a matter of such difficulty as to be practically impossible. We have not determined the actual Ca and HPO_4 ions in the serum but it is obvious that a situation similar to that with silver chloride must be present. There must be a solubility product constant for Ca and HPO_4 ions which has a definite value at a given pH

and temperature. When this constant is exceeded precipitation must take place. When the calcium ion concentration is very low no precipitation can occur and when the HPO_4 ion concentration is very low there will likewise be no precipitation because there is a definite physiological limit of increase of concentration for each ion in the serum. The calcium cannot increase indefinitely to compensate for a low phosphorus concentration and the phosphorus cannot increase indefinitely to compensate for a low calcium concentration.

While the ionic concentration cannot be measured we can prove that the general principle holds true by clinical observation using as factors for a rough product the total concentration of calcium and of phosphorus in the serum. We may also approach the question by means of certain chemical experiments.

If we multiply the concentration of the calcium by the inorganic phosphorus concentration, each expressed in milligrams per 100 cc. of serum we obtain a product which with the normal child is between 50 and 60 and with the rat about 80. When the product is below 30 rickets is invariably present. When it is above 40 either demonstrable healing is taking place or there has never been any rickets. With products between 30 and 40 rickets is usually present. In a large series we have found only one case of healing with a product between 30 and 40. Perhaps this was the result of a poor determination.

Marriott and I, and more recently Kramer and I have approached the subject of calcification experimentally. We have made artificial serum with the same amount of sodium bicarbonate, magnesium and sodium chloride that normal serum contains. We have added varying amounts of calcium and phosphorus and we have kept the solutions at a constant temperature subjected to a carbon dioxide tension to give any desired pH. When precipitation has occurred we have frequently determined the composition of the precipitate. The solutions may be made up with or without a colloid such as gelatine.

In our experiments the pH of the solution has been made to vary, usually between 7.35 and 7.45. The calcium concentration has not been above the normal maximum, i.e., 11 mgm. and the inorganic phosphorus not above 5.5 mgm. per 100 cc. of fluid. But the con-

centrations have been altered so as to produce different products. We have kept the solutions at 37.5°C. and have determined the presence or absence of precipitation at the end of twenty-four and forty-eight hours.

Precipitation may be brought about in a number of different ways such as increasing the pH by reducing the CO_2 tension, by increasing the temperature and by altering the calcium and phosphorus concentrations. When the pH is about 7.35 and the product of the concentrations of Ca and P is 40 or more a precipitate always forms. The precipitate is composed chiefly of tricalcium phosphate. It apparently makes no difference in the result or in the character of the precipitate if the calcium is 8 and the phosphorus 5 or the calcium 10 and the phosphorus 4 mgm. per 100 cc. When the product is less than the numbers mentioned no precipitate forms. Refinements of technique remain to be worked out and the influence of colloids must particularly be studied. The experiments are not easy on account of the difficulty in adjusting the pH satisfactorily. This is most important because a very slight difference in the pH has a profound effect. Yet enough has been accomplished to show that even in a complicated solution such as this artificial serum, precipitation depends directly upon the product of the concentrations of Ca and P in the solution.

We may visualize calcification somewhat in this way. Serum contains calcium and inorganic phosphorus in solution in much higher concentration than water would hold them on account of the high CO_2 tension. There is some evidence to show that part of the calcium is bound to protein. If it is assumed that this calcium-protein compound is poorly ionized this would be equivalent to reducing the total calcium concentration. Intercellular fluid of the tissues contains roughly the same amount of calcium and phosphorus, according to our determinations, as the serum, but the protein is much less, apparently about 1 per cent as contrasted with the 7 to 9 per cent in the serum. The CO_2 tension is relatively high on account of cellular activity. But supposing that the CO_2 tension is low because the tissue is inactive or dead, then conditions are favorable for precipitation. Cartilage and the trabeculae of bone are both inactive tissues and it is in them that one would expect the CO_2

tension low and it is in them that precipitation takes place. We do not know accurately the changes in reaction between arterial and venous blood but the difference in reaction of perhaps 0.02 of a pH is sufficient to determine the site of precipitation. Nature has performed experiments for us in that peculiar condition known as metastatic calcification which demonstrate this. In metastatic calcification there is great bone destruction going on and therefore it is probable that the serum is saturated with the salts of bone. Precipitation of calcium salts takes place in those parts of the body where acid is given off that is in the lungs, the stomach and the kidneys. It is very striking, however, that this precipitation occurs always on the arterial side of the capillaries never on the venous side.

In a trabecula of bone the salts are deposited in the center and not at the periphery. There is always a layer of osteoid tissue on the outside, a rim of uncalcified material. This points to greater ease of precipitation at the point most removed from active tissues. One might ask why the whole of the epiphyseal cartilage is not calcified as all of it is inactive. This apparently depends upon the blood supply. Liek has proved in experiments on the calcification of the rabbit's kidney that a moderately free circulation is necessary in order that this should occur. The epiphyseal cartilages are poorly supplied with blood. The cartilage canals that perforate the cartilage bend down toward the epiphyseal line and the arteries contained in them do not subdivide until just before the line is reached. The portion of the cartilage that becomes impregnated with lime salts lies between these smaller vessels and the loops of blood vessels that extend up from the marrow. It is intimately in contact with blood vessels. Each trabecula of bone is also well surrounded by blood vessels.

Calcification is facilitated in the child because during his growing years his serum has a higher inorganic phosphorus concentration than that of the adult. But when the phosphorus falls as it does in rickets a point is reached where precipitation is impossible. An increase of calcium cannot compensate for the low phosphorus because, as has repeatedly been shown, the calcium concentration of the serum cannot be increased beyond its normal limits. Calcium

introduced in any way, even intravenously, is promptly eliminated. Similarly in tetany, the reduction of calcium necessary to cause symptoms of activity cannot be compensated for by any phosphorus concentration which the serum of the child with normal kidneys can maintain. With the increase of the inorganic phosphorus of the serum that results from treatment, conditions approach the normal and eventually allow calcification to occur again.

This view of the factors that control and of the mechanism of calcification explains the normal process and the failure in rickets and tetany of children and the rickets of animals. It also explains calcification in dead or inactive tissues such as tuberculous lesions and in the fascial planes of the muscles in myositis ossificans where the first change seems to be a hyaline transformation of the connective tissue. What is further of much importance it explains the constancy of composition of the bones of all animal species in which the calcium and inorganic phosphorus concentrations of the serum so far as they have been studied do not differ greatly from those of man. It also explains why the composition of the inorganic salts of rachitic bones is like that of normal bone. Brubacher, Gassmann and several others including ourselves have found this to be true with children. McCann and Barnett demonstrated that the salts of the bones of rachitic rats, irrespective whether they developed rickets upon a low calcium or a low phosphorus diet, were similar to those of normal bones. Elliot, Crichton and Orr found the salts of the bones of normal and rachitic pigs to be similar. From the heterogeneous mixture of salts in normal serum or in our artificial serum a precipitate is formed chiefly of calcium phosphate with a little calcium carbonate.

One further subject remains for discussion. Why is the inorganic phosphorus concentration of the serum low in rickets? Emphasis may justly be laid upon the phosphorus because it is this substance which is regularly reduced in uncomplicated rickets and it is the lack of a sufficient amount of phosphorus that, in our opinion, is chiefly responsible for the failure of calcification. It is impossible, however, to consider phosphorus independently of calcium, their association is so intimate and the influence of the one upon the other so definite.

The present evidence is all in favor of the view that defective absorption is the important factor. With a diet of cow's milk, the food which most children who become rachitic are receiving, the absorption and retention of mineral elements is less than with woman's milk even though the total intake is much higher with the former than with the latter. In this connection the experiments of Oeri may be remembered which point to the fact that milk added to the ordinary diet of the adult increases very greatly the amount of phosphorus excreted in the stools.

The *reaction* within the intestinal tract has a strong influence. Alkalies as Gerhardt and Schlesinger have shown diminish mineral absorption and acids, according to Schetelig increase it. The stools of infants receiving cow's milk are usually alkaline or far less acid than when a child receives woman's milk.

When cow's milk is diluted, as it usually is in the first few months of the infant's life, the fat is lower than in woman's milk and of course in condensed milk mixtures so commonly the diet of the rachitic child, the fat is strikingly low. Hoobler, Giffhorn and Telfer have shown convincingly that the absorption of phosphorus is very poor when the fat of the diet is diminished and that the absorption rises progressively with an increase of the fat. Holt and Fales have shown recently that the same is true of the calcium absorption. Telfer has emphasized that with an increase of fatty acids in the stools there is an increase of phosphorus excretion by the kidneys which speaks for better absorption. There are more than enough metabolism experiments on animals and children to show that calcium added to the diet increases the fecal excretion of phosphorus and conversely that alkaline phosphates increase the excretion of calcium. This fact is utilized in composing the diets to render animals rachitic. The low phosphorus diet contains an excess of calcium above the optimum amount for the animal and vice versa. As the result of an increase of one element or as the result of some alteration of reaction in the intestinal tract or perhaps from some unknown cause the solubility of calcium and phosphate compounds is exceeded and precipitation occurs. Excretion by the intestinal tract follows. Mellanby could discover no favorable influence upon the rickets of dogs when tricalcium phosphate was given in the food.

There are metabolism experiments on the effect of treatment with cod liver oil by Schabad and E. Schloss which show unmistakably that the effect of the oil is to increase absorption. Normally 70 per cent or more of the phosphorus excreted by the breast fed infant appears in the urine and with the child on cow's milk about 60 per cent. With rickets the conditions are quite reversed: much the larger part may be excreted by the bowel. When recovery is taking place a return to normal occurs; the phosphorus of the urine may be quite unchanged in amount but that of the feces is greatly reduced. Retention occurs at the expense of the fecal phosphorus. The effect upon the calcium absorption is similar but the results are not so plain because the majority of the calcium in health or disease is excreted by the intestine. The results with rats also indicate the same process. Upon a diet so low in calcium or phosphorus that rickets results, animals grow slowly and eventually die. When 3 per cent of cod liver oil is included in their diet they not only grow well but they raise the element that has been deficient in their serum nearly if not quite to the normal concentration. Moreover, they are capable of reproduction to the third or fourth generation. An animal of the first generation from some hidden store or by some more economical method of utilization might build up her own tissues but she could not furnish the material for three or four generations of animals. The conclusion seems unavoidable that better absorption is responsible. In the case of children Schabad recognized this long ago. If cod liver oil taken by mouth brings about this better absorption how do sunlight and ultra violet radiation raise the phosphorus and calcium of the serum? The answer is also: by better absorption, at least this seems the logical deduction to be drawn from the experiments of Orr, Holt, Wilkins and Boone. A marked increase of the retention of both phosphorus and calcium followed systematic radiation. This increased retention was accompanied by a marked reduction of the calcium and phosphorus excreted in the stools. It would be premature as well as unwise to try to go farther and say why these dissimilar therapeutic agents are capable of bringing about a cure in the same way.

Just one word about the future: Rickets has had its day. It will be stamped out or least reduced to insignificant proportions.

Indeed it is in the process of being stamped out. It is only the magnitude of the problem that makes it difficult. Hess and Unger showed what could be accomplished with an experimental area in New York. The whole city has to be included in such a program and so has nearly every large city of Europe and America. The people as well as physicians must be educated. It is rather striking how far the process of education has already advanced. We do not see nearly so many severe forms of rickets as we did ten or even five years ago. It is no unusual experience to have a poor woman in an outpatient clinic ask if it is not now about time to begin giving her child cod liver oil. The next generation of physicians will not have the unlimited opportunity for the study of rickets and tetany that has been ours yet no one will mourn the disappearance of rickets.

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ANTIKETOGENESIS: ITS MECHANISM AND SIGNIFICANCE[1]

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It is common knowledge that when any human subject fasts there appears, on the second or third day, acetone in his breath and acetone, acetoacetic and hydroxy butyric acids in his urine. These same substances are excreted in large amounts also by severe diabetics, and the two organic acids are responsible for the acidosis and coma characteristic of this disease. The growth of our knowledge of these three substances, the so-called "acetone bodies" is a long and interesting story, much too long and perhaps too well known to justify any attempt at its restatement here. A comprehensive review has been written by Magnus Levy (a) (1908).

That part of the subject which I am invited to discuss here is a field in which I have been working during the last few years and has to do first, with the mechanism by which normal individuals avoid the formation, or at any rate the accumulation of these substances, and second with the application of our ideas of this mechanism to the metabolism of human subjects with ketosis and the attempt to formulate in quantitative terms those factors which determine when and how much acetone bodies will be formed and excreted. Although the evidence at hand does not permit a very exact statement, the principles involved appear to be considerably clarified and there is promise of a correct understanding of many points which have heretofore been obscure. Indeed now for the first time, it appears to be possible to predict with some measure of confidence the degree of ketosis which a subject will develop under certain circumstances; and what is more important from a practical

[1] A lecture delivered before the Harvey Society of New York February 10, 1923.

point of view, it becomes possible *to state in quantitative terms, the character of the metabolism which must be maintained to avoid ketosis.*

Without attempting a review of literature on the acetone bodies, the main points may be outlined in a few words. Passing over the early work and shifting points of view as to their derivation, it is now well established that the three acetone bodies have a common origin, two of them being merely products of the third which represents a normal stage in the break-down of certain other molecules in the body. The first formed of the acetone bodies is very probably aceto-acetic acid, which if it accumulates in the body is in part decomposed into acetone and CO_2 and in part is reduced to hydroxy butyric acid. The appearance of the acetone bodies is therefore essentially the production or accumulation of a keto-acid, a ketosis; and those substances which are the precursors of the acetone bodies are termed ketogenic or ketoplastic. Two different classes of food constituents are known to be convertible into acetoacetic acid: the higher fatty acids of neutral fat and a few of the amino acids of protein. The work of Schwarz, Geelmuyden, Magnus Levy, Knoop, Embden, Dakin and others leaves no doubt that straight chain fatty acids with an even number of carbon atoms (in natural fats) in the course of their catabolism pass through the stage of β-keto or hydroxy butyric acid. But it is also well established that glycerol, the other component of natural fats, is not convertible into acetone but in the diabetic (Cremer, Luthje), and probably in the normal subject also, is converted into glucose. Similarly the amino acids of protein fall into two classes; leucin, tyrosin, phenylalanine, and possibly histidin and others giving rise to acetoacetic acid (Borchardt and Lange, Embden, Baer and Blum, Dakin) while glycocoll, alanine and a number of others are convertible into glucose (Lusk, Dakin). Still other amino acids as lysine and tryptophane appear to take neither course.

Normal subjects normally fed do not excrete the acetone bodies, except in inconsiderable traces. They appear in largest quantities in severe diabetes, and with normal subjects only when fasting or when the food carbohydrate is greatly restricted. Hirschfeld in 1895 first showed that the factor common to these conditions and responsible for the ketosis is the absence of carbohydrate from the

food, or as in the diabetic, from his metabolism. This idea has been fully substantiated and there is today no question that ketosis is due to carbohydrate starvation. The burning of sugar in the body in some way prevents the appearance of ketosis, and is therefore antiketogenic. Many other substances also have been found to inhibit ketosis, and are therefore classed as antiketogenic (Satta). Prominent among such substances are glycerol and those amino acids which when fed to diabetics are converted into glucose. In the absence of any evidence to the contrary, it may be reasonably assumed that they exert their antiketogenic effect after conversion into glucose, and are therefore effective only to the extent that glucose or its equivalent is formed from them. Indeed it is doubtful whether any substance not convertible into glucose has been shown conclusively to exert direct antiketogenic action. Alcohol which has been advocated as a food for severe diabetics is not an exception, for its occasional effect in reducing ketosis can be explained by simple replacement for ketogenic fat in the material burned.

It appears therefore that the fragments of food material metabolized in the body may be divided into two distinct classes which have opposing influences upon the appearance of acetoacetic acid and ketosis. The ketogenic group, the fatty acids and several of the amino acids, pass through the stage of acetoacetic acid. Here their oxidation stops unless a sufficient amount of the other group of antiketogenic carbohydrate and glucose-forming substances is simultaneously being oxidized. The *oxidation* of glucose is evidently essential, because the severe diabetic, forming glucose from protein, but failing to burn it, is the best manufacturer of keto acid.

The facts above briefly outlined have long been known and have been stated repeatedly in convincing fashion. They point clearly to a chemical reaction between some oxidation product of glucose and one of the acetone bodies or its precursor, as the explanation of the inhibiting effect of carbohydrate upon ketosis. It would seem that the facts can be explained in no other way. A number of hypotheses have been based in general upon these considerations, but until a few years ago there was no direct satisfactory evidence of the existence of a chemical reaction of the sort assumed and doubtless for that reason, no one of the hypotheses was developed or applied to the problems

of human metabolism, and the interesting and important consequences of the idea remained undiscovered.

The notion of a "secondary oxidation" suggested by Nasse and elaborated by Naunyn, and the much quoted phrase of Rosenfeld that "Fats burn only in the fire of carbohydrates" suggest some sort of chemical reaction, but, as Magnus Levy (a, p. 396) says, are descriptive, not explanatory. A more definite idea was advanced by Geelmuyden (b) in 1904, to the effect that some one of the acetone bodies which is normally produced in the course of metabolism in the cells reacts with a product of glucose (glycuronic acid) and that failing such synthesis, as in the absence of glucose, the acetone body would accumulate and be excreted. In its general outline this conception was undoubtedly correct and adequate to explain the facts, but in the absence of definite evidence in its support, the idea received but scant consideration and appears to have been abandoned by its author. (See Geelmuyden, d, 1923). A somewhat similar hypothesis was put forth by Woodyatt in 1910, that "antiketogenesis is an effect due to certain products which occur in the oxidation of glucose, and interaction between these products on the one hand and one or more of the acetone bodies on the other." But Woodyatt likewise was not able to advance evidence of such interaction, and further application of the idea was not made.

In 1914 Ringer presented the hypothesis that "the rôle of glucose in the normal individual in preventing acidosis to be such as to deviate the β-hydroxy butyric acid from its ordinary course of oxidation, by combining with it and thereby changing its structural configuration so as to give rise to non-acetone genetic products." The experimental basis for this hypothesis was the finding by Ringer and Frankel that acetaldehyde and propylaldehyde when given subcutaneously to diabetic dogs resulted in a rise of glucose excretion accompanied by a fall in the acetone body excretion. The coincident increase of glucose with the fall of total acetone was interpreted by Ringer to indicate the conversion of hydroxybutyric acid into glucose as a result of the reaction. Later work by Sansum and Woodyatt in which they took precautions to rid the animals of all glycogen, failed to show extra sugar or a decrease of ketosis from acetaldehyde injection, and these authors therefore decline to accept Ringer's

interpretation of his results. Somewhat the same view as that of Ringer has been lately adopted by Geelmuyden (d), who now believes that either acetone bodies or sugar may be formed from fat, and favors the old idea of Minkowski that ketonuria represents a derangement of sugar synthesis.

The sharp distinction between ketogenic and antiketogenic substances has been brought into question also by the ideas of Embden and others as to their interconversion by way of acetic aldehyde. But in spite of this recent trend of opinion, the earlier view of Geelmuyden and Woodyatt and Ringer, that a reaction takes place between one of the acetone bodies and a product of glucose, was undoubtedly correct. This was indicated by the fairly definite relationship between the amounts of carbohydrate versus fat which produce ketosis.

In studying the effect of low carbohydrate diets, Zeller found (1914) that acetone first appeared when the food contained 80 grams carbohydrate and 310 grams fat, and concluded that one part of carbohydrate is required for the complete combustion of four parts of fat. And from an analysis of these data Lusk (1917) suggested that each molecule of hydroxybutric acid required the presence of one triose molecule. Woodyatt (1916) citing the same data, concluded that "when the mixture of metabolites oxidizing in the body contains more than three molecules of higher fatty acids to one of glucose, then the body 'smokes' with acidosis compounds like an automobile smokes with too much oil in the cylinders." Lang (1915) found that when the ratio of fat to carbohydrate oxidized rises above a minimum value of 2 grams of fat to 1 of carbohydrate abnormal quantities of acetone appear. Ladd and Palmer find with diabetics ratios between 4 and 2 grams of fat to 1 gram of glucose. Counting the glycerol of fat as 0.5 molecules of glucose, the molecular ratios would be, approximately:

	mols. fatty acid : mols. glucose
Zeller (Lusk-Woodyatt)	= 2 : 1
Lang	= 1 : 1
Ladd and Palmer (diabetics)	= 2 : 1 and 1 : 1

These ratios take no account of the influence of protein, but they indicate that acetonuria first appears when the mixture of fat and

carbohydrate burned contains between 1 and 2 molecules of fatty acid for each molecule of total glucose.

But the view nevertheless persisted that different degrees of ketosis observed with different subjects depend upon unknown "individual peculiarities." For example, Joslin (1917) discusses the "adaptation of the body to a non-carbohydrate diet and to starvation" and Folin and Denis describe the "habituation to the complete oxidation of mobilized body fat" resulting from repeated fasts.

THE IN VITRO KETOLYTIC REACTION

With the conviction that antiketogenesis must have its explanation in a reaction between glucose and some ketogenic substance and that this reaction should be capable of demonstration in the test tube if the right conditions could be hit upon, I have experimented at intervals during a period of many years, with glucose in the presence of each of the three acetone bodies and of butyric acid and other substances in the hope of finding an antiketogenic action. The results were uniformly negative and discouraging until the combination of glucose and acetoacetic acid in strongly alkaline solutions containing hydrogen peroxide was tried. This is, of course, the combination that might have been first selected, for glucose readily oxidizes in alkaline solution and acetoacetic acid besides being the first formed of the acetone bodies, is much the most reactive one. But no one else appears to have tried it, and I hit upon it only after many useless experiments. In the presence of glucose undergoing oxidation there is a rapid disappearance of acetoacetic acid, much more rapid than in the absence of glucose. With suitable concentrations of alkali and peroxide and with an excess of glucose practically all of the acetoacetic acid may be destroyed in one hour or less at room temperature, while without glucose much of the acetoacetic acid may resist oxidation for more than twenty-four hours. Here evidently was the long sought reaction, a close analogy to the behavior of glucose in the body in inhibiting ketosis (Shaffer, 1921). The essential factor in the *in vitro* reaction, as in the body, is the *oxidation* of glucose. Alkali is essential *in vitro* for the oxidation of glucose by air or H_2O_2.

In neutral or acid solutions there is no oxidation of glucose and no consumption of keto acid occurs; and in the absence of peroxide the

consumption is relatively very small. The rate of the consumption increases with the concentration of alkali and of glucose and with temperature. The definite relationship between the amount of keto acid destroyed and the amount of glucose oxidized shows that a chemical reaction occurs in definite molecular ratios between an oxidation product of glucose, and acetocetic acid. Evidently the glucose is first "dissociated" (Nef) by the alkali, and this product is oxidized to a substance which reacts with acetoacetic acid to form a compound which is further oxidized. The disappearance of the acetoacetic acid results from a train of dependent reactions, the rate of which is primarily limited by the action of alkali in dissociating the glucose. This is shown by the fact that the rates of (1) loss of reducing power, (2) acid production and (3) the disappearance of acetoacetic acid are apparently the same. The concentration of alkali in limiting the rate of glucose oxidation may be compared with the effect of the pancreas in limiting glucose tolerance (Woodyatt, 1915).

With the assistance of T. E. Friedemann this ketolytic reaction has been studied in considerable detail. It has turned out to be a complicated matter and many points are yet obscure. We have studied the rates and products of the reaction with glucose and other hexoses, and with related substances such as glyceric aldehyde, glycol aldehyde, glyoxal, acetaldehyde and formic aldehyde. I shall state here only a few points of greatest interest.

Acetoacetic acid in the form of its ethyl ester has long been known as an exceedingly valuable substance for the ready synthesis of a great variety of organic compounds. Among the various synthesis are its well known reactions with aldehydes which have been studied especially by Knövenagel, who showed that under different conditions 1 molecule of the aldehyde combines with either 1 or 2 molecules of the ester, forming mono- and bis-alkylidine acetacetic esters of the types

$$CH_3—CO—\underset{\underset{HC-R}{\|}}{C}-COO—C_2H_5 \quad \text{and} \quad CH_3—CO—\underset{\underset{HC-R}{|}}{CH}-COO—C_2H_5$$

$$CH_3—CO—\underset{\underset{CH_3—CO—CH-COOC_2H_5}{|}}{CH}-COOC_2H_5$$

A large number of different aldehydes of both the aliphatic and aromatic series have been used in such syntheses. Because of its ease of decomposition the free acetoacetic acid is not suitable for the purpose, and apparently has not been so used; but we find that in the form of its alkali salt it condenses as does the ester with aldehydes. Simultaneously with the condensation the keto acid loses its carboxyl group by splitting off CO_2 and the rate of CO_2 production may serve to indicate the rate of condensation. This behavior of acetoacetic acid, long known for its esters, of condensing with aldehydes, doubtless furnishes the clue to the explanation of our *in vitro* ketolytic reaction and in all probability of the antiketogenic action of glucose in the body as well. Glucose itself shows no such reaction, either in the body or in the test tube; it must first be "dissociated" and *oxidized.*

THE KETOLYTIC DERIVATIVE OF GLUCOSE

What is the product of glucose which condenses with acetoacetic acid? This question is of considerable importance because it is possibly this substance which the diabetic is unable to form from glucose, and the absence of which is responsible for ketosis. We are not yet able to answer the question with certainty, though some of the possibilities can be excluded.

When glucose is acted upon by alkali it is converted, according to Nef, into more than a hundred different substances, of which more than half are fragments of the sugar molecule. The first substances formed are very unstable and pass rapidly to secondary end products such as lactic acid. The final products of these reactions are not ketolytic. It is therefore *an oxidation product of some intermediate transitory substance which reacts with acetoacetic acid.*

Simple aldehydes, such as formic and acetic aldehyde, combine with acetoacetic acid, and if formed from glucose *in vitro* or from its metabolism in the body, might be regarded as the ketolytic agents. Both these substances have been claimed to be glucose intermediates. The prominence assigned by Neuberg, (1913) Embden (1922) and others to acetic aldehyde in carbohydrate metabolism, the experiments by Ringer (1914) on acetic aldehyde and antiketogenesis, the claim of its conversion into glucose by diabetic dogs (Ringer (1914),

Benedict (1922)) and the finding of traces of aldehyde in diabetic urine (Stepp) and in muscle (Hirsch) all serve to direct attention to its possible rôle in antiketogenesis.

But in spite of this evidence, I cannot believe that it has any part in the ketolytic action of glucose either *in vitro* or in the animal body. The reaction of acetic aldehyde with acetoacetic acid is very slow and incomplete compared with the behavior of the products of glucose. Based upon the slow rate of its reaction it is therefore excluded as a possible *in vitro* ketolytic derivative of glucose. Furthermore, we have been unable to find any indication of its formation from glucose under the conditions of the *in vitro* ketolytic experiments. The claim by Schade that it is formed from glucose by alkali was later admitted by him to be incorrect.

According to Neuberg, Embden and others acetic aldehyde is formed in the body from the oxidation of glucose, by the following scheme: Glucose → lactic acid → pyruvic acid → acetic aldehyde + CO_2. The acetic aldehyde is supposed then to have either of two opposite effects. According to Friedmann (1908) two molecules may condense to aldol and yield acetoacetic acid, *thus increasing ketosis by an immediate product of carbohydrate metabolism.* Or, according to Ringer it may react with acetoacetic acid and thus reduce ketosis. The reactions are supposed also to be reversible, acetic aldehyde serving as a bridge over which glucose is converted to fatty acid or vice verse (see Neuberg's review, 1913). This conception is a very handy device to explain variations in ketosis in either direction; but, as a whole, the conception is certainly wrong. A quantitative analysis of the conditions under which ketosis appears in human subjects (Shaffer, 1922) *affords no ground for the belief that products of carbohydrate metabolism are precursors of the acetone bodies* (except when carbohydrate is converted into fat). Ketosis exists only when the amount of carbohydrate metabolized is *small*, and is *decreased or abolished when the amount of carbohydrate metabolized is increased.* It seems therefore that one must discard either the notion that acetic aldehyde is formed from glucose in animal metabolism, or that if so formed it is converted into acetoacetic acid. Furthermore, the fact that all degrees of ketosis can be adequately explained without resort to a bridge between ketogenic and antiketogenic substances

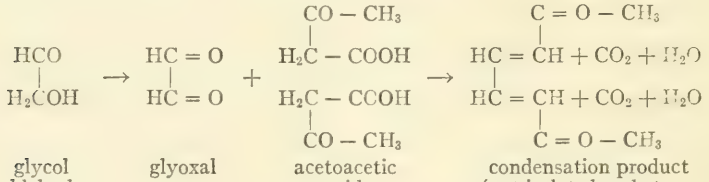
makes it very doubtful whether such interconversion takes place. (The last statement must be qualified by recalling the undoubted formation of fat from carbohydrate which occurs during carbohydrate plethora. Evidence appears to be opposed to the reverse transformation. In so far as either conversion may take place, there is no indication that they have direct and immediate effect upon the appearance or degree of ketosis.)

The formation of acetic aldehyde in yeast fermentation (Neuberg) is established, as is the formation of acetone, butyl alcohol and butyric acid from glucose by different microörganisms (Speakman), but these facts scarcely justify the belief that these substances are formed from glucose in the animal body. It is stated (Reizenstein, cited by Fricke) that acetic aldehyde, like acetone, is quite resistant to oxidation in the body, yet the amounts found in urine are exceedingly small. It seems to me improbable that acetic aldehyde is a main product of glucose oxidation in the body; some other substance is much more likely to be the ketolytic agent.

Prominent among the intermediates of glucose, both *in vitro* and in the body, is methyl glyoxal. It is formed by the action of alkali on glucose (Neuberg and Oertel) and is according to Dakin, Neuberg, Levene and others an intermediate in the reversible reactions,

glucose ⟷ methyl glyoxal ⟷ lactic acid, in the body.

Although we have not tested methyl glyoxal we find that in neutral or faintly alkaline solution the related glyoxal is markedly ketolytic, condensing rapidly with two molecules of acetoacetic acid. Glycol aldehyde, also, when oxidized by hydrogen peroxide in alkaline solution, under which conditions it passes through the stage of glyoxal likewise reacts with 2 molecules of the keto acid.



glycol aldehyde — glyoxal — acetoacetic acid — condensation product (not isolated and structure is hypothetical)

These facts point to methyl glyoxal as the ketolytic derivative of glucose. But such a conclusion would be erroneous, at least for the

in vitro reaction for the following reasons. Methyl glyoxal is produced from glucose by the action of alkali without oxidation, but glucose requires oxidation for its ketolytic action. In spite of the undoubted formation of methyl glyoxal in alkaline solutions of glucose there is under such conditions very little effect upon acetoacetic acid. Oxidation is necessary. The methyl glyoxal formed (by alkali alone) is doubtless prevented from reacting with keto acid by its very rapid conversion to lactic acid, which occurs with great speed in the presence of alkali. Another argument in opposition to methyl glyoxal became apparent on comparing the behavior of glucose and of glyceric aldehyde *in vitro*. With both substances (in the presence of alkali, H_2O_2 and an excess of acetoacetic acid) *1* molecule of the aldose accomplishes the removal of *2* molecules of acetoacetic acid,[2] but with alkali alone there is formed from 1 molecule of glyceric aldehyde only one-half as much lactic acid (and of its precursor methyl glyoxal) as from 1 molecule of glucose. From this it follows that methyl glyoxal cannot be the ketolytic intermediate in these reactions.

In the body it is supposed that each molecule of glucose is converted into 2 molecules of lactic acid (Meyerhof, 1920), *via* glyceric aldehyde and methyl glyoxal. If glucose were to exert its antiketogenic (ketolytic) action through its conversion to methyl glyoxal (2 molecules) and if the latter were to react in the body with acetoacetic acid in the same proportions which glyoxal and glyceric aldehyde do *in vitro*, each molecule of glucose would be expected to furnish ketolytic substance for a maximum of 4 molecules of keto acid. But as we shall see glucose has only about half that antiketogenic action. It may therefore be concluded that the antiketogenic or ketolytic derivative of glucose, both in the *in vitro* reaction and in the body, is probably not methyl glyoxal but an earlier oxidation product, which reacts with 2 molecules of acetoacetic acid for each molecule of glucose oxidized. If this view is correct it points to an oxidation of glucose before its splitting into 2 molecules of glyceric aldehyde, methyl glyoxal and lactic acid as pictured in the conven-

[2] In the first paper (Shaffer, 1921, I) the molecular ratio between glucose and keto acid consumed was given as 1:1, but later work showed that in the presence of an excess of keto acid 2 molecules disappear for each molecule of glucose oxidized.

tional views concerning the pathway of glucose oxidation (Neuberg, 1913; Embden, 1922).

Apart from the validity of such arguments as cited above the fact appears to be established that glucose and related hexoses when dissociated by alkali and oxidized pass at one stage through a substance (or substances) which condenses with 2 molecules of acetoacetic acid, if the latter be present in excess, the product being further oxidized. With this *in vitro* ketolytic reaction as a model, the attempt was made to learn whether the avoidance of ketosis by human subjects could be adequately accounted for by the hypothesis of a similar reaction in the body.

THE KETOGENIC BALANCE IN MAN

If antiketogenesis is the result of a definite chemical reaction, between constant proportions of the reacting substances, one would expect that so long as glucose is being metabolized in excess, in relation to the rate of formation of acetoacetic acid, all of the latter would disappear as fast as formed and no ketosis would result. But, whenever the number of molecules of metabolizing glucose is insufficient to react with all of the acetoacetic molecules, the excess would accumulate and be excreted. Between these extremes there would be a condition when the glucose burned just balanced the acetoacetic acid, and this should be near the borderline of very slight ketosis.

The testing of this idea required that an estimate be made in terms of molecular quantities of the total amounts of all precursors of acetoacetic acid, the ketogenic factors and of glucose and glucose-formers, the "antiketogenic factors," in the metabolic mixture. According to the hypothesis the ratio between these quantities should determine whether or not the subject would show ketosis. I shall first outline very briefly the assumptions adopted for the calculation of these ketogenic *versus* antiketogenic factors. Existing information does not permit very exact estimates of their numerical value and they will doubtless require considerable revision.

Ketogenic factors. Each molecule of fatty acid catabolized is assumed to give rise to one molecule of acetoacetic acid (Magnus Levy, 1901). Taking 874 as the molecular weight of mixed food or body-fat, 1 gram of such fat would correspond to 3.43 millimols of

ketogenic material. The amino acids leucin, phenylalanine and tyrosin, probably histidin and possibly others are converted into acetoacetic acid. Using Osborne's Analysis as modified by Lusk (1915) of muscle protein, we calculated that 1 gram of nitrogen of protein corresponds to 10 millimols of the first three amino acids and to that amount of ketogenic material. This estimate was later arbitrarily increased to 15 millimols of ketogenic precursors for 1 gram of nitrogen (Shaffer, 1922, p. 406). The sum of the ketogenic values of fatty acid and of protein represents the total precursors of acetoacetic acid derivable from any given mixture of metabolism.

Antiketogenic factors. The glucose equivalents of carbohydrate, of the glucose-forming amino acids, and of the glycerol of fat are calculated, and expressed in gram molecules of glucose. One gram of glucose = 5.56 millimols of glucose. Since protein is convertible into glucose to the extent of 3.6 grams for each gram of nitrogen, 1 gram of nitrogen is equivalent to $\frac{3.6}{180} \times 1000 = 20$ millimols of glucose. One gram of fat contains $\frac{1}{874} \times 1000 = 1.14$ millimols of glycerol, which on conversion to glucose would equal 0.57 millimol.

If there can be determined what amounts of fat, carbohydrate and protein are being burned in the body, it is a simple matter to calculate, by use of these factors, how much acetoacetic acid would be formed and how much glucose burned according to these assumptions. And by choosing subjects with very slight ketosis, we can learn the ratio at the borderline of ketosis. Actually the calculation is beset with many difficulties and errors. There is no very reliable way of knowing just what or how much is being oxidized in the body, or that the proportions in different parts of the body are the same or constant throughout the period of observation. At best we can expect only rough approximations to the facts. But by making a number of reasonable assumptions, it is possible to obtain an estimate on which to base the calculations. If the total calories of metabolism are known, or can be assumed, one can subtract the calorie value of the protein (urine nitrogen) and of the carbohydrate burned, the remainder representing fat. When the carbohydrate in-

take is small, the amount eaten can be assumed to be the amount burned. The largest error is probably in the estimates of the total metabolism, from which the fat must be calculated. Even if the resting or basal metabolism is determined, the total energy exchange for the day is quite uncertain.

The following example will illustrate the manner of making the calculations. F. G. Benedict's (1915) fasting subject "L" on the second day of the fast excreted about 0.5 gram of hydroxy butyric acid. Benedict calculated from respiratory data that the total metabolism for the twenty-four hours was 1756 calories obtained from the combustion of 142 grams fat, 42 grams glycogen and protein corresponding to 8.4 grams of urine nitrogen. Using the factors above stated, such a mixture would represent the following quantities of ketogenic and antiketogenic material, the latter calculated in terms of glucose.

	KETOGENIC MILLIMOLS	GLUCOSE MILLIMOLS
8.4 gram N	126 (8.4 × 15)	168 (8.4 × 20)
142 gram fat	487 (142 × 3.42)	81 (142 × 0.57)
42 gram CH		233 (42 × 5.56)
	613	482

Ratio ketogenic to glucose millimols = 1.27

The same calculation of data for the first fast day with the same subject, when no ketosis existed gives a ratio below 1.

	KETOGENIC MILLIMOLS	GLUCOSE MILLIMOLS
7.1 gram N	105.5	142
135 gram fat	463	77
68.8 gram CH		383
	568.5	602

Ratio ketogenic to glucose millimols = 0.94

From an analysis of similar data from a number of different subjects (mostly from the literature) the conclusion seemed to be justified that ketosis appears when the ratio of ketogenic molecules to total

antiketogenic molecules, calculated as glucose, in the mixture being metabolized exceeds 1:1 (Shaffer, 1921, c). A few of the data are summarized in Table 1.

The matter was later investigated by Woodyatt (1921) and by Hubbard and Wright (1922), using the same fundamental assump-

TABLE 1

Data representing ketogenic balance near threshold of ketosis

(From calculations by Shaffer (II and IV))

AUTHOR	SUBJECT	KETOGENIC MILLIMOLS	TOTAL GLUCOSE MILLIMOLS	RATIO $\frac{\text{KETOGENIC MILLIMOLS}}{\text{TOTAL GLUCOSE MILLIMOLS}}$	KETOSIS GRAMS TOTAL ACETONE	FOOD CH GRAMS
Zeller	Normal	777	631	1.2	+ slight	Low CH diet
Lang	Normal	831	665	1.2	0.3	60
Lang	Normal	786	894	0.9	0	100
Ascoli Preti	Normal	613	507	1.2	0.6	30
Ascoli Preti	Normal	599	573	1.0	0.3	45
Krogh	Eskimo	905	1283	0.7	0 (?)	54
Shaffer	Non-diabetic	682	524	1.3	0.77	38
Shaffer	Non-diabetic	630	685	0.9	0.18	75
Hubbard and Wright	Normal case I	923	687	1.3	1–2	50
Hubbard and Wright	Normal case I	870	1000	0.87	±0.1	100
Benedict	"L" 1st fast day	568	602	0.94	0	Fasting
Benedict	"L" 2nd fast day	613	482	1.27	±0.5	Fasting
Voit, standard diet		462	4172	0.1	0	Normal diet

tions which I had earlier outlined. Their results confirmed the conclusion just stated. The composition of diets which produce ratios of about 1:1 is: at least 10 per cent of the total calorie requirement as carbohydrate, about 10 per cent as protein and not more than 80 per cent as fat.

It was next shown (Shaffer, 1921, III) that the same conclusion is reached from an analysis of the respiratory quotients of subjects

at the borderline of ketosis. The details of the method of analysis involve many figures and will be omitted here. The same underlying assumptions as to the ketogenic value of protein and fat and the glucose equivalent of protein, fat and carbohydrate were applied to respiratory data by well known principles.

According to the analysis a respiratory quotient of 0.76 represents the combustion of a mixture containing approximately equal quantities of ketogenic and total glucose molecules. And it was found, as a rule, that the respiratory quotient of different subjects at the threshold of ketosis is about 0.76. With higher quotients there was no ketosis, and with lower quotients usually a marked ketosis. We have followed the respiratory metabolism at intervals during three to five day fasts with a number of normal subjects, and find that although the quotients often vary unaccountably, the first appearance of acetone in the breath and of acetoacetic acid in urine is most commonly observed at quotients near 0.76. The respiratory data therefore seem to indicate a ratio of about 1:1 at the threshold of ketosis.

It was noted, however, that when the ratio of ketogenic molecules to glucose was somewhat greater than 1, not nearly as much acetoacetic acid (total) was excreted as would be expected from the calculated excess, based on a 1:1 ratio for the ketolytic reaction. For example, the calculation for the second fast day of Benedict's subject L, cited above, gave 613 ketogenic millimols and 482 millimols of glucose, and a ratio of 1.27. If 1:1 were the minimum ratio, there would be an excess of 131 millimols of acetoacetic acid over available glucose, corresponding to 13 grams of keto or hydroxy butyric acid. But only about 1 gram was excreted. Some subjects may, indeed, as shown by data reported by Wilder and Winter (1922) have little or no ketosis in spite of ratios considerably above 1:1. Ladd and Palmer's ratio of 4 grams fat to 1 gram carbohydrate (which corresponds to a molecular ratio of fatty acid to glucose of about 2:1) was also significant. This discrepancy, noted in my first analysis (Shaffer, II, 466) indicated that some of the assumptions were wrong and pointed to the probability that the ketolytic ratio in the body is greater than 1:1. On reconsideration especially of data from subjects with severe ketosis, it was found (1922, IV) that the amount

of total keto acid excreted in severe ketosis corresponds fairly closely with the calculated expectation, based upon a ratio of 2 molecules of keto acid destroyed for 1 molecule of glucose burned, the same ratio which had been found in later work with the *in vitro* reaction. Although the errors involved in the calculations are large there can scarcely be doubt that when the metabolic mixture is such as to yield a very large excess of ketogenic molecules over the number of glucose molecules burned the amount of total keto acid which is excreted approximately corresponds to the excess over and above *twice* the total glucose molecules burned. This was shown to be, in general, true for the ketosis developed by more than twenty different subjects, normals fasting and on low carbohydrate diets, and severe diabetics. Most of the data to be found in the literature as well as our own results, have been analyzed, and while the agreement is often not as close as might be desired, the results seem to show that the most important factors leading to ketosis are accounted for, and at least roughly evaluated.

The following examples will illustrate the method of calculation and the nature of the assumptions which are necessary.

Forssner has reported (1909) valuable experiments upon himself. During a period of eighteen days during which the daily diet consisted of 163 grams protein, 306 grams fat and 300 cc. of wine, with a total caloric value of 3600, he excreted from 3 to 13 grams of total hydroxy butyric acid. The urinary nitrogen averaged 23 grams. A recalculation of his data during this period shows that the ketogenic ratios were close to 2:1, which is in accord with the degree of ketosis. With a high protein diet this normal subject derived almost enough glucose from protein to balance his keto acid production. On the nineteenth day he fasted and on the twentieth and twenty-first ate only butter and bacon. The protein metabolism fell to half the previous level and the ketosis increased on the last two days to 34 and 43 grams total acid per day. On the last two days one may assume that no glycogen was available and that only protein and fat were burned. Taking the total metabolism at 3000 calories, and subtracting the caloric value of the protein metabolized (urine N $\times$ 26.5 calories) we have the caloric value of fat burned. The ketogenic balance may be drawn up as follows. It is clear that the rather

severe ketosis is fairly well accounted for provided we assume a rather high total metabolism and correspondingly high fat combustion.

Forssner

	KETOGENIC MILLIMOLS	GLUCOSE MILLIMOLS	
Twentieth day			
Protein (12 grams N)	180	240	1102—(401 × 2) = 300 excess ketogenic or 31 grams hydroxy butyric acid expected. 34.3 grams excreted
Fat (2682 calories)	922	161	
	1102	401	
Twenty-first day			
Protein (11 grams N)	165	220	1149—(382 × 2) = 385 excess ketogenic or 40 grams total hydroxy butyric expected. 42.8 grams excreted.
Fat (2710 calories)	984	162	
	1149	382	

The data from the severe diabetic "Cyril K" recorded by Gephart, Aub, DuBois and Lusk may be used as another example. On December 18, fasting, the urine contained 20 grams nitrogen, 55 grams glucose and 58 grams hydroxy butyric acid. The resting metabolism was determined, 73.2 calories per hour. Taking 110 per cent of this value, we obtain 1935 calories as the probable total heat production in twenty-four hours. Adding the calorie value of glucose and keto acid excreted we have 2414 calories representing the metabolism of all material, some of which was not burned. Since no glycogen or food carbohydrate was burned, we may learn the fat combustion by subtracting protein calories from total calories. (2414 − (20 × 26.5) = 1884 fat calories.) The ketogenic balance then stands as follows:

	KETOGENIC MILLIMOLS	GLUCOSE MILLIMOLS
Protein (20 grams N)	300	400
Fat (1884 calories)	684	113
Deduct for 55 grams glucose derived from protein and glycerol		−306
	984 − 207 × 2 = 570	

570 × 0.104 = 59 grams acid expected
58 grams + excreted

TABLE 2

AUTHOR	SUBJECT	DESCRIPTION	DAYS	KETOGENIC MILLIMOLS	TOTAL GLUCOSE MILLIMOLS	RATIO $\frac{K}{G}$	EXCESS KETOGENIC MILLIMOLS	TOTAL HYDROXY BUTYRIC ACID		
								Expected	Excreted	
Benedict	"L"	Normal fasting	27	532	243	2.19	46	4.8	6.0	Average of 27 days (5–31) of fast
Means, Folin, Denis	Mrs. McK	Obese woman fasting	2	786	288	2.7	210	22.0	22.6	Average of 3 and 4 day of first fast
	Mrs. McK	Obese woman fasting	1	680	204	3.3	272	28.3	17.3	5th day of 2nd fast
	Mrs. McK	Obese woman fasting	1	663	188	3.5	287	29.8	20.1	4th day of 3rd fast
Grafe	M. K.	Fasting, catatonic stupor	5	517	174	3.0	169	17.6	14.5	Average of 5 days (15–19) of fast
Wilder-Winter		Epileptic fasting	1	586	213	2.7	160	16.6	10.2	11th day of fast
DuBois-Lusk	Cyril K.	Severe diabetic	8	1010	167	6.0	676	70.2	55.0+	Average October 15–22
Joslin	No. 740	Moderate diabetic	9	581	222	2.6	137	14.2	10.6	Average April 15–May 1
Mosenthal-Lewis	E. W.	Severe diabetic	8	897	136	6.6	625	65.0	79.0	Average December 3–10
Shaffer	Kramer	Severe diabetic	14	872	154	5.6	565	58.8	62.0	Average of 14 days
Forssner (1909)	Self	Normal, fat diet	1	1002	401	2.5	300	31.0	34.3	20th day
Forssner (1909)	Self	Normal, fat diet	1	1149	382	3.0	385	40.0	42.8	21st day

In Table 2 the results from the analysis of other cases are summarized. (The data are averages of results of calculations made in a former paper, which contains the references; Shaffer, 1922, IV.)

It will be noted that the figures for total hydroxy butyric acid show rather striking agreement between the amounts predicted and actually excreted.

From these results it would appear that when there is a large surplus of keto acid molecules in the body to react with all available ketolytic molecules, the reaction is approximately quantitative in that all of the glucose burned exerts its maximum ketolytic action. And this maximum appears to be 2 molecules of keto acid for 1 of glucose.

When a large surplus of keto acid is not being formed it would be expected that some glucose molecules would be oxidized without encountering and reacting with keto acid, and thus the ketolytic value would be wasted; while at other localities there might be a deficit of glucose with consequent accumulation of keto acid. Such a condition exists, we may imagine, near the threshold of ketosis, when, due to uneven distribution and uneven metabolism in different parts of the body, considerably more than the theoretical minimum of glucose is necessary to avoid ketosis. According to this view one might expect that the amount of the excess required to avoid ketosis would vary from the theoretical minimum to a considerably higher value. This expectation is borne out by the facts. Many subjects show slight ketosis with a metabolic ratio of 1 ketogenic to 1 total glucose, while considerable higher ratios may exist without very marked ketosis. Wilder and Winter have emphasized this fact. As a rule, however, the higher the ratio above 1:1 the more pronounced the ketosis until at 2:1 or above the amounts of total hydroxy butyric acid excreted are large and approximate more and more to the excess of keto acid over glucose calculated on a 2:1 ratio. The range between ratios of 1:1 and 2:1 is variable in that either very small or moderate ketosis may result.

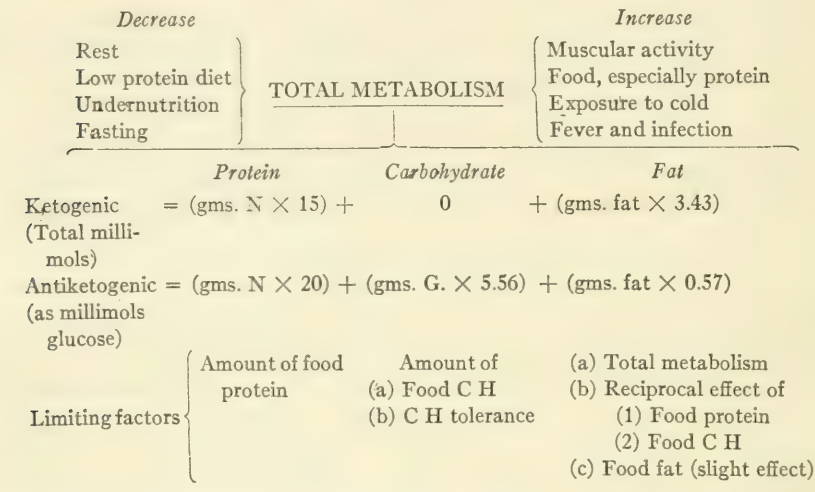
THE APPLICATION OF THE KETOGENIC BALANCE TO METABOLISM IN DIABETES

If the evidence presented be accepted as justifying the conclusion that antiketogenesis is the result of a reaction between definite pro-

portions of ketogenic and ketolytic substances, and if it be granted that the evaluation of the respective influence of fat, protein and carbohydrate is approximately correct, there follows as a necessary consequence a clearer conception of the metabolism in diabetes and of the dietetic treatment of this disease. The brilliant results already secured from the use of insulin give promise of radical changes in methods of treatment of diabetes, but dietetic methods will doubtless remain of fundamental importance.

The primary aim of the dietetic treatment is to restrict the amount of carbohydrate metabolized to within the subject's tolerance, in order to avoid its overstrain and further loss. The consequence of too great a restriction is qualitatively the same as great loss of tolerance—the development of ketosis, the *bete noir* of the disease. The problem therefore is to regulate the inflow of all glucose forming foods below the rate at which the subject can burn (or store) it, and above the rate necessary to provide sufficient ketolytic material to avoid ketosis. The width of the margin between these extremes, very great with normal subjects and narrower with diabetics, represents the factor of safety possessed by the individual. *One of these extremes, the total glucose minimum or the ketolytic minimum is defined by the ketogenic balance;* the other extreme is the total glucose tolerance. If a safe margin over the "total glucose minimum" be supplied and burned, there appears to be no reason to expect ketosis. *The formulation of an optimum diet is therefore the calculation of such a mixture of fat, protein and carbohydrate as will adequately nourish the subject by supplying a metabolic mixture which complies with the requirements as to ketogenic* versus *antiketogenic influences.* Several formulae have been proposed for this diet calculation, based upon the conception of ketogenic ratios. I shall not attempt their explanation, but will refer those interested to the papers by Woodyatt, (1921), Wilder (1922), Hubbard and Nicholson (1922) and myself (1922). The point to be emphasized in connection with these formulae and diet calculations is that it is the mixture oxidized, and not necessarily the food eaten which determines ketosis, and I believe this fact will be better borne in mind, and with clearer understanding, if we do not make too many short cuts in the diet calculation.

The metabolic mixture consists of fragments of amino acids from protein, of fat and of sugar. The exact composition of this mixture and the resultant of its ketogenic balance will depend upon those factors which determine how much of each flows into the metabolic stream, in relation to the total rate of flow, that is, to the total metabolism. The influence of these various factors may be illustrated by the accompanying diagram.


Decrease
Rest
Low protein diet
Undernutrition
Fasting
TOTAL METABOLISM
Increase
Muscular activity
Food, especially protein
Exposure to cold
Fever and infection
Protein
Carbohydrate
Fat
Ketogenic (Total millimols) = (gms. N × 15) + 0 + (gms. fat × 3.43)
Antiketogenic (as millimols glucose) = (gms. N × 20) + (gms. G. × 5.56) + (gms. fat × 0.57)
Limiting factors
Amount of food protein
Amount of (a) Food C H (b) C H tolerance
(a) Total metabolism
(b) Reciprocal effect of (1) Food protein (2) Food C H
(c) Food fat (slight effect)

There are four main terms in the equation represented by the diagram, (1) total metabolism, (2) protein, (3) carbohydrate, (4) fat, each of which is in some degree affected by the others, but is chiefly influenced by different factors.

The total metabolism is mainly determined by the subject's size or surface area, by muscular activity, by the plane of nutrition, and by such abnormal factors as fever and infection. The effect of food intake, although distinct, is probably of minor (immediate) importance. The total energy exchange continues at the pace set by the first named factors, even in fasting, and is increased after food only to the extent of its so-called specific dynamic effect (Lusk, 1922). The effect of protein is large, of fat and carbohydrate much smaller. With maintenance diets the increase amounts to about 10 or 15 per cent of the fasting metabolism.

The factors which determine the *relative participation* of protein, carbohydrate and fat in the total combustion are in large part different from those which decide the total metabolism. The immediate factor is probably the relative abundance (concentration?) of their fragments in the blood or in the cells. That which is most readily available is burned. The source of supply is of course the food. Above a certain minimum, the amount of protein fed is approximately the amount catabolized (nitrogen equilibrium), and within limits the flow of protein fragments is therefore controlled by the diet. The amount of carbohydrate burned is likewise, within limits, determined by the amount of carbohydrate fed. Up to the limit of tolerance it replaces fat without very markedly increasing the total metabolism. When the amount fed is small or when capacity to burn it is low as in diabetes, fat and to some extent protein fragments are used instead.

The amount of food fat on the other hand has less influence upon the amount of fat burned. If the flow of food fat decreases, the body fat is drawn upon instead.

With an increase in the fat fed there is to be sure a stimulation of fat combustion due to fat plethora (see Lusk, 1922) and the experiments of Forssner indicate that this is accompanied by an increase in keto acid production. But both these effects are of a lower order than results from changes in protein or carbohydrate ingestion.

The points to be emphasized are:

1. That the total metabolism is the result of somewhat inexorable requirements, to a large extent (but not wholly) independent of food supply. Food protein markedly stimulates metabolism; fat and carbohydrate do so only to a slight degree.

2. That the amounts of protein and carbohydrate burned are controlable by the diet, and

3. That the amount of fat burned is to a large extent independent of diet, and depends chiefly upon how much additional fuel, besides protein and carbohydrate, is needed to keep up the total metabolism.

When, as in diabetes, the lowered carbohydrate tolerance places an upper limit upon the rate at which glucose, whatever its origin, can be burned, the *ketogenic balance will be determined primarily by the factors which control fat combustion, namely, by the height of the*

total metabolism and by the amount of protein fed. A given carbohydrate tolerance may allow the formation of enough ketolytic substance to neutralize the keto acid formed from 1500 calories and 50 grams of protein, but not enough to avoid ketosis when the metabolism is 2500 calories with 100 grams of protein.

From this point of view it seems to me that the first question to decide for a case of diabetes is not (as calculated by Woodyatt) how much fat can be allowed in his diet, for that is a secondary matter, but *how much extra glucose, in the form of food carbohydrate, is necessary in order to provide a safe margin over a ketogenic balance.*

This is the base line *below which the total glucose tolerance* cannot fall without ketosis, and the relation of the subject's tolerance to this base line is the measure of severity of his disease. If this minimum amount of food carbohydrate be calculated for the subject's rate of total metabolism and for his plane of protein metabolism, and this amount be supplied *and burned*, ketosis should not occur.

The simple qualitative tests of the urine for sugar and for acetoacetic acid have, in the light of this conception, a clearer significance. The absence of both shows an adequate *supply* of total glucose and an adequate carbohydrate *tolerance* for ketogenic balance at the existing rate of total metabolism.

The presence of acetoacetic acid without glycosuria means an inadequate *supply* of carbohydrate (total glucose). Glycosuria without ketosis means a lowered carbohydrate tolerance, but that the tolerance is above the ketogenic base line for the existing rate of metabolism.

When both keto acid and glucose are present, the tolerance is at once shown to be below the minimum necessary for the rate of that subject's total metabolism. With such a condition *only* two courses would seem to be possible: either the carbohydrate tolerance may be raised by insulin or the total metabolism must be lowered by rest, low protein diets, under nutrition or fasting, until the rate of keto acid production no longer exceeds the tolerance. Either push one side of the ledger up or pull the other side down, until they balance.

In order to learn the ketogenic base line for any given subject a relationship must be calculated between rates of total metabolism and the corresponding minima of antiketogenic metabolism. A

formula expressing this relationship is easily calculated from the ketogenic and antiketogenic factors of fat, carbohydrate and protein (see diagram, p. 396). According to these factors protein is both ketogenic and antiketogenic, but is predominately antiketogenic, and the excess will "neutralize" some keto acid from fat. By subtracting from the total calories of metabolism the calories of protein (Urine N) + the calories of fat neutralized by the excess of protein, we have left the calories of metabolism which must be supplied by fat and carbohydrate in such ratio that the antiketogenic influence of carbohydrate will at least equal the excess ketogenic influence of fat. The equation which I evolved (1922, IV) for this relationship is:

$$\text{Minimum food CH} = \frac{\text{Total cal. of metabolism} - (\text{urine N} \times 100)}{50}$$

The result from this equation is the theoretical minimum of carbohydrate and a variable margin above this minimum is always necessary to prevent ketosis. Double the amount appears usually to suffice. If the carbohydrate tolerance does not allow the combustion of this amount ketosis will be unavoidable, until the tolerance is raised or the total metabolism is lowered.

The amount of food protein should be moderately low: for adults 0.75 gram per kilogram is probably sufficient. The amount of food fat allowed depends upon how much additional fuel is needed to maintain energy equilibrium. It may be considerably reduced if undernourishment is desired, but the amount fed has only a minor influence upon the type of metabolism and the liability to ketosis.

For practical use one may either use the above formula for calculation or construct a chart from which the results can be read off directly. A clever and convenient chart based upon the same underlying considerations and yielding approximately the same results (and including the separate calculation also of protein and fat) has recently been devised by Wilder. Another has been described by Hannon and McCann. The accuracy of any of these formulae depends upon the correctness of the assumptions and evaluations upon which they rest. Further experience and more accurate data will doubtless demand their revision, and may show that other factors must be taken into consideration. But in the meanwhile they are

of real value because they give more definite quantitative expression to the various factors in the metabolism of diabetes than has previously been possible.

The conception of antiketogenesis upon which they are based defines the lower limit of total carbohydrate tolerance and allows its approximate calculation for any given subject, at the rate of his total metabolism. The difference between this calculated base line and the subject's tolerance is the measure, at least from the theoretical view point, of his factor of safety—when the difference is on the right side; or measures the margin of danger, when the base line is crossed. The conception helps to explain the benefits and the limitations of modern dietetic treatment as enunciated by Allen, Joslin, Newburgh and Marsh, and Woodyatt and forms the basis for the recent proposals of Wilder. By defining how much the tolerance must be raised it offers additional criteria for the administration of insulin and the determination of its effect.

Always a fascinating field for the biochemist, diabetes remains the favorite testing ground for theories concerning intermediary products of metabolism and their inter-relations. Without this disease some of our most interesting speculations would have remained unknown, and from its further investigation we may hope to learn how far these speculations are statements of fact.

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